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(54) Title: NOVEL EPOXIDE-CONTAINING COMPOUNDS

$$- (CH_2)_n -C - C - (CH_2)_j - CH_3, \quad (I)$$

with epoxide O over the C—C bond.
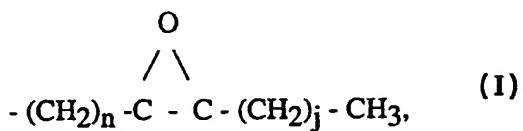
(57) Abstract

Compounds comprise epoxide-substituted alkyl side chain (R) bonded to a core moiety, comprising Core moiety (I), wherein n is an integer from about 4 to about 16 and j is an integer from about 0 to about 12, including resolved enantiomers and/or diastereomers, salts, solvates, hydrates and mixtures thereof. Preferably, n is an integer from about 4 to about 12, more preferably from about 4 to about 10. j is preferably an integer from about 0 to about 3. The alkyl groups may also be substituted by a hydroxyl, halo or dimethylamino group and/or interrupted by an oxygen atom, H or alkyl (1-4C).

NOVEL EPOXIDE-CONTAINING COMPOUNDS

Technical Field of the Invention

The invention relates to a class of epoxide-containing therapeutic compounds that act
as drugs on the cellular and biochemical level to modulate cellular responses to noxious,
proinflammatory stimuli. More specifically, the inventive compounds have at least one
epoxide group on a side chain bonded to a core moiety.

Background of the Invention

Pentoxifylline (1-(5-oxohexyl)-3,7-dimethylxanthine), abbreviated PTX, is a xanthine
derivative which has seen widespread medical use for the increase of blood flow. PTX is
disclosed in U.S. Patents 3,422,307 and 3,737,433. Metabolites of PTX were summarized in
Davis et al., *Applied Environment Microbiol.* 48:327, 1984. A metabolite of PTX is 1-(5-
hydroxyhexyl)-3,7-dimethylxanthine, designated M1. M1 was also disclosed as increasing
cerebral blood flow in U.S. Patents 4,515,795 and 4,576,947. In addition, U.S. Patents
4,833,146 and 5,039,666 disclose use of tertiary alcohol analogs of xanthine for enhancing
cerebral blood flow.

Furthermore, U.S. Patent 4,636,507 describes an ability of PTX and M1, to stimulate
chemotaxis in polymorphonuclear leukocytes in response to a stimulator of chemotaxis. PTX
and related tertiary alcohol substituted xanthines inhibit activity of certain cytokines to affect
chemotaxis (U.S. Patent 4,965,271 and U.S. Patent 5,096,906). Administration of PTX and
GM-CSF decrease tumor necrosis factor (TNF) levels in patients undergoing allogeneic bone
marrow transplant (Bianco et al., *Blood* 76: Supplement 1 (522A), 1990). Reduction in
assayable levels of TNF was accompanied by reduction in bone marrow transplant-related
complications. However, in normal volunteers, TNF levels were higher among PTX
recipients. Therefore, elevated levels of TNF are not the primary cause of such
complications.

Therefore, there is a need in the art to discover effective therapeutic compounds that
are safe and effective for human or animal administration and that maintain cellular
homeostasis in the face of a variety of inflammatory or noxious stimuli. The invention
results from investigations of such compounds.

Summary of the Invention

We have found that the compounds described herein can be used to maintain
homeostasis of a large variety of target cells in response to a variety of stimuli. In addition,
the inventive compounds and compositions are suitable for normal routes of therapeutic
administration and permit effective dosages to be provided.

The invention is directed to epoxide-containing alkyl side chains bonded to a core
moiety useful in modulating cellular response to external or *in situ* primary stimuli, as well as
to specific modes of administration of such compounds in effective amounts.

The inventive compounds comprise epoxide-substituted alkyl side chain (R) bonded to a core moiety, comprising:

$$Core\ moiety - (CH_2)_n -C\ \overset{O}{\overset{/ \backslash}{-}}\ C - (CH_2)_j - CH_3,$$

wherein n is an integer from about 4 to about 16 and j is an integer from about 0 to about 12, including resolved enantiomers and/or diastereomers, salts, solvates, hydrates and mixtures thereof. Preferably, n is an integer from about 4 to about 12, more preferably from about 4 to about 10. J is preferably an integer from about 0 to about 3. The alkyl groups may also be substituted by a hydroxyl, halo or dimethylamino group and/or interrupted by an oxygen atom, H or alkyl (1-4C).

The core moiety may be a heterocyclic or a non-heterocyclic moiety. A non-heterocyclic moiety is, for example, an amino acid (one or two), an hydroxyl group, a carboxyl group, a sulfoxide group, a sulfonate group, a phosphate group, an amide, an amine, a ketone, a simple ionic functional group, a terminal hydrogen or halogen atom. Exemplary core moiety amino acids may include one or more of the following: alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. The core moiety may preferably be a dipeptide comprising two amino acids selected from the foregoing exemplary list. Exemplary halogen atoms include bromine, chlorine, fluorine and iodine.

Exemplary heterocyclic core moieties may be substituted or unsubstituted, and preferably may include, but are not limited to, substituted or unsubstituted phthalimide, homophthalimide, quinazolidinedione, quinazoline, xanthine, glutarimide, piperidine, piperidone, γ- valerolactam, cyclohexane, cyclohexene, benzene, uracil, thymine, uracil fused to napthalene, ortho-phenol, imidazole amide, pyrrole amide, benzamide, tetrahydrophthalimide or succinimide. Preferred heterocyclic core moieties may contain at least one ring nitrogen atom, the R side chain being bonded to a ring nitrogen. For example, the heterocyclic moiety may be xanthine, phthalimide, thymine, alkyl-substituted (C1-6) thymine, uracil, alkyl-substituted (C1-6) uracil, glutarimide, 2,5,4'-trihalobenzophenone, 1,4-trihalomethylbenzamide (preferably the halogen groups are selected from chloro, bromo, iodo and fluoro) and resorcinol. More preferably, the heterocyclic core moiety may be 1,7-methylxanthine, 8-amino-3-methylxanthine, 7-methylhypoxanthine, dimethyldihydroxypyrazolo[4,3-d]pyrimidine, methylpyrrolo[2,3-d]pyrimidine, 5- and 6-substituted uracils, 6-aminouracil, 2,4-dioxohexahydro-1,3,5-triazine, methylbarbituric acid, isocarbostyril, 1,2,3,4-tetrahydroisoquinolin, 2-hydroxypyridine, 3,3-dimethylflutarimide, 1,3-dihydroxynapthalene, 1,3-cyclopentanedione, 2-pyrrole amide, 3-pyrrole amide, 1-pyrrole amide and substituted benzamides. Preferable compounds of the invention, having

a xanthine core moiety, may include, but are not limited to, compounds having a single epoxide-substituted alkyl side chain (R) at position 7 of the xanthine nucleus.

The invention includes a method for modulating an immune response or a cellular response to external or *in situ* primary stimuli comprising administering an effective amount

5   of an inventive compound. Particularly, on a cellular or biochemical level, the inventive compounds have been found to inhibit a specific phospholipid-based pathway that amplifies a signal within a cell. This pathway tends to be activated in response to noxious or inflammatory stimuli. The inventive compounds also decrease proliferation of tumor cells in response to an activated oncogene; stimulate hematopoiesis in the presence of agents which

10   inhibit hematopoiesis, such as chemotherapeutic agents; suppress the activation of T-cells in the presence of antigen and the secretion of antibodies by B-cells in the presence of antigen; suppress the activation of macrophage or endothelial cells by endotoxins, tumor necrosis factor (TNF), interleukin-1 (IL-1) or granulocyte macrophage colony stimulating factor (GM-CSF); enhance the resistance of mesenchymal cells to TNF; inhibit the proliferation of

15   smooth muscle cells, endothelial cells, fibroblasts and other cell types in response to growth factors, such as platelet derived growth factor (PDGF), PDGF-AA, PDGF-BB, fibroblast growth factor (FGF), epidermal growth factor (EGF), etc.; inhibit the activation of T-cells and viral replication in response to human immunodeficiency virus; inhibit the proliferation of kidney mesangial cells in response to IL-1; prevent suppression of Steel factor (also called

20   stem cell factor, mast cell growth factor and kit ligand), granulocyte colony stimulating factor (G-CSF), oncostatin M or interleukin-6 (IL-6) in bone marrow stromal cells in response to TNF; suppress expression of adhesion molecules in endothelial cells and suppress adhesion of inflammation cells to endothelial cells; suppress proliferation of kidney mesangial cells in response to IL-1, mip-1α, PDGF or FGF; prevent toxicity in kidney

25   glomerular or tubular cells in response to cyclosporin A or amphotericin B; prevent cytotoxic effects in gastrointestinal or pulmonary epithelial cells in response to a cytotoxic drug or radiation; enhance the antitumor effects in tumor cells in response to a nonalkylating antitumor agent; suppress the production of metalloproteases in synovial cells, other fibroblasts and a glomerular epithelial cell in response to inflammatory stimuli, such as TNF,

30   IL-1 and the like; inhibit production of osteoclast-activating factor (OAP) by osteoclasts in response to IL-1; inhibit degranulation of mast cells and basophils in response to IgE; modulate signal transduction of the neurotransmitters epinephrine and acetylcholine in neural pathways utilizing these transmitters. block activation of platelet activating factor in inflammation cells, block release of TNF and IL-1 in various cell types in response to

35   inflammatory stimuli, block activation and proliferation of lymphocytes and other cell types to IL-1 and interleukin-2 (IL-2), and the like, including the clinical manifestations of these cellular and biochemical events.

In vitro, the inventive compounds: 1) block IL-1 signal transduction through the Type 1 receptor as shown, for example, by preventing IL-1 and IL-1 plus PDGF (platelet

derived growth factor) induction of proliferation of smooth muscle and kidney mesengial cells; 2) suppress regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD18 in neutrophils; 3) inhibit TNF, LPS and IL-1 induced metalloproteases (an inflammation model); 4) block LPS, TNF or IL-1 induced cellular
5   activation (for prevention and treatment of septic shock); 5) suppress T cell and B cell antigen activation by cross-linking CD3 complex; 6) inhibit mast cell activation by IgE; and 7) suppress malignant phenotype in transformed cells and tumor cell lines.

The inventive compounds, *inter alia*, inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as IL-1 antagonists. Dinarello
10 and Wolff, "The Role of Interleukin-1 in Disease," *N. Engl. J. Med.* 328, 106 (Jan. 14, 1993), describe the role of IL-1 as "an important rapid and direct determinant of disease." "In septic shock, for example, IL-1 acts directly on the blood vessels to induce vasodilatation through the rapid production of platelet activating factor and nitric oxide, whereas in autoimmune disease it acts by stimulating other cells to produce cytokines or enzymes that
15 then act on the target tissue." *Ibid.* The article describes a group of diseases mediated by IL-1, including many of the foregoing diseases.

In still another aspect, the invention is directed to a pharmaceutical composition comprising an inventive compound and an effective amount of an agent which reduces the activity of the enzyme P-450, such as a quinolone, to increase the pharmacokinetic half-life
20 of an inventive compound.

Brief Description of the Drawings

Figure 1 shows a mixed lymphocyte reaction of three inventive compounds CT1605 (N-(5,6-oxidohexyl) glutarimide), CT1808 (N^3-(5,6-oxidohexyl)-N^1-methyluracil), and CT1906 (N^3-(5,6-oxidohexyl) N^1-methylthymine). The mixed lymphocyte reaction shows a
25 proliferative response of PBMC (peripheral blood mononuclear cells) to allogeneic stimulation determined in a two-way mixed lymphocyte reaction. Each of the inventive compounds tested was effective (and more potent than PTX although not shown on this graph) in this immune modulating activity assay procedure.

Figure 2 shows a comparison of three dose levels of CT1808 and CT1906 and no
30 drug control to inhibit thymocyte proliferation. The thymocytes were obtained from normal female Balb/C mice and stimulated with Concanavalin A (Con A) and/or interleukin-1 alpha (L-1α). Drugs were added to the cell cultures two hours before activation with Con A and/or IL-1α. As shown in Figure 2, both drugs inhibited thymocyte proliferation is a dose-dependent fashion.
35 Figure 3 shows a comparison of CT1605 and CT1808 on inhibition of B-cell proliferation. A Ramos C-cell tumor line was treated with 250 μM CT1808 or CT1605 for one hour prior to stimulation of proliferation with anti-mu antibody or phorbol myristic acid (PMA, 5 nM). One day later, proliferation was measured with tritiated thymidine. Both CT1605 and CT1808 inhibited proliferation in this model.

Figure 4 shows a comparison of CT1605, CT1808 and CT1906 on PDGF-induced (platelet derived growth factor) proliferation of human stromal cells. Human stromal cells were starved in serum-free media for 24 hours and then stimulated with 50 ng/ml of PDGF-BB. The drugs were added at various indicated concentrations one hour prior to PDGF
5   stimulation. Tritiated thymidine was added for 24 hrs at the time of PDGF stimulation to measure cellular proliferation. Background counts were approximately 5% of control levels. All three drugs inhibited PDGF-induced stimulation in a dose response fashion.

Figure 5 shows the effect of CT1605, CT1808 and CT1906 to inhibit adhesion of U937 cells to activated human umbilical vein endothelial cells (HUVEC). HUVEC cells
10   were activated with 20 ng/ml of TNF for 12 hrs. Drug was added to each culture (except for controls) one hour prior to adding TNF. U937 cells, preloaded with the fluorescent dye BCECF, were added to each culture well and then washed. Cell adhesion was determined on a fluorescence plate reader, showing a decrease in cell adhesion caused by all three drugs in a dose dependent fashion.

15   Figure 6 shows the effects of CT1605, CT1808 and CT1906 to inhibit cell surface expression of VCAM in human umbilical vein endothelial cells (HUVEC). The HUVEC cells were stimulated with 20 ng/ml TNF-α for 20 hrs and then stained for immunofluorescence using a monoclonal antibody recognizing VCAM, followed by a goat anti-mouse antibody conjugated to phycoerythrin. The cells were analyzed for antibody
20   binding using flow cytometry. Figure 6 shows an analysis of mean relative fluorescence intensity of 10,000 cells, analyzed by flow cytometry. The mean fluorescence levels were decreased by all three drugs from control levels (TNF treatment, no drug).

Detailed Description of the Invention

The invention is directed to a defined genus of inventive compounds which can
25   control cellular behavior by a particular phase of a secondary messenger pathway system (Bursten et al., J. Biol. Chem. 266:20732, 1991). The second messengers are lipids or phospholipids and use the following abbreviations:

PE = phosphatidyl ethanolamine

LPE = lysophosphoethanolamine

30   PA = phosphatidic acid

LPA = lysophosphatidic acid

DAG = diacylglycerol

LPLD = lysophospholipase-D

LPAAT = lysophosphatidic acid acyl transferase

35   PAPH = phosphatidic acid phosphohydrolase

PLA2 = phospholipase A-2.

PLD = phospholipase D

PAA = phosphoarachidonic acid

PLA-2 = phospholipase A2

PC = phosphatidyl choline

"remodeled" PA, cyclic pathway = PAA, LPA, PA and DAG intermediates substituted with L-saturated, 2-linoleoyl or 1,2-dileolyl/1,2-sn-dilinoleoyl at the indicated sn-1 and sn-2 positions.

"Classical PI Pathway" = PI, DAG, PA intermediates substituted with 1-stearoyl, 2-arachidonoyl fatty acyl side chains.

"PLD-generated PA" = PE, PC, LPA, PA and DAG intermediates substituted with, e.g., 1,2-sn-dioleoyl-, 1-alkyl, 2-linoleoyl-, and 1-alkyl, 2-docosahexaneoyl-side chains.

Lysophosphatidic acid transferase (LPAAT) effects the synthesis of phosphatidic acid (PA) from lysophosphatidic acid (LPA) by incorporation of an acyl group from acyl CoA. Hydrolysis of the phosphate moiety by PA phosphohydrolase (PAPH) results in the formation of DAG. These aspects of the pathway appear to be activated immediately (within a minute) upon stimulation by a primary stimulus (e.g., a cytokine such as interleukin-1 or TNF) acting at a receptor on a cellular surface. An immediate detectable effect is an elevation of levels of PA and DAG. Administration of the compounds of the invention reverse this elevation.

The compounds of the invention, include inhibitors of subspecies of LPAAT in PAPH enzymes with substrate specificity for intermediates with 1,2-diunsaturated and 1-alkyl, 2-unsaturated subspecies. One representative example of such an inhibitor (although not within the genus of inventive compounds) is PTX. PTX blocks PAPH in a specific activation pathway that does not involve PI but rather derives from a PA that is largely composed of 1,2-diunsaturated and 1-alkyl,2-unsaturated subspecies. This was shown, for example, by the demonstration that human mesangial cells stimulated with TNF produce DAG from PI and regenerate PI in the absence and the presence of PTX. In the latter system there is no evidence to suggest that PA or DAG are derived from sources other than PI. It should be emphasized that the compounds of the invention affect that subset of PAPH and LPAAT that relates to substrates with unsaturated fatty acids other than arachidonate in the sn-2 position, not the housekeeping forms of these enzymes that serve the PI pathway.

Compounds of the Invention

The inventive compounds comprise epoxide-substituted alkyl side chain (R) bonded to a core moiety, comprising:

$$\text{Core moiety - (CH}_2)_n \text{ -C} \overset{\displaystyle O}{\overset{\displaystyle /\backslash}{-}} \text{C - (CH}_2)_j \text{ - CH}_3,$$

wherein n is an integer from about 4 to about 16 and j is an integer from about 0 to about 12, including resolved enantiomers and/or diastereomers, salts, solvates, hydrates and mixtures thereof. Preferably, n is an integer from about 4 to about 12, more preferably from about 4 to about 10. J is preferably an integer from about 0 to about 3. The alkyl groups may also be

substituted by a hydroxyl, halo or dimethylamino group and/or interrupted by an oxygen atom, H or alkyl (1-4C).

The core moiety may be a heterocyclic or a non-heterocyclic moiety. A non-heterocyclic moiety is, for example, an amino acid (one or two), an hydroxyl group, a

5   carboxyl group, a sulfoxide group, a sulfonate group, a phosphate group, an amide, an amine, a ketone, a simple ionic functional group, a terminal hydrogen or halogen atom. Exemplary core moiety amino acids may include one or more of the following: alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine

10   and valine. The core moiety may preferably be a dipeptide comprising two amino acids selected from the foregoing exemplary list. Exemplary halogen atoms include, but are not limited to, bromine, chlorine, fluorine and iodine.

Exemplary heterocyclic core moieties may be substituted or unsubstituted, and preferably may include, but are not limited to, substituted or unsubstituted phthalimide,

15   homophthalimide, quinazolidinedione, quinazoline, xanthine, glutarimide, piperidine, piperidone, γ- valerolactam, cyclohexane, cyclohexene, benzene, uracil, thymine, uracil fused to napthalene, ortho-phenol, imidazole amide, pyrrole amide, benzamide, tetrahydrophthalimide or succinimide. Preferred heterocyclic core moieties may contain at least one ring nitrogen atom, the R side chain being bonded to a ring nitrogen. For example,

20   the heterocyclic moiety may be xanthine, phthalimide, thymine, alkyl-substituted (C1-6) thymine, uracil, alkyl-substituted (C1-6) uracil, glutarimide, 2,5,4'-trihalobenzophenone, 1,4-trihalomethylbenzamide (preferably the halogen groups are selected from chloro, bromo, iodo and fluoro) and resorcinol. More preferably, the heterocyclic core moiety may be 1,7-methylxanthine, 8-amino-3-methylxanthine, 7-methylhypoxanthine,

25   dimethyldihydroxypyrazolo[4,3-d]pyrimidine, methylpyrrolo[2,3-d]pyrimidine, 5- and 6-substituted uracils, 6-aminouracil, 2,4-dioxohexahydro-1,3,5-triazine, methylbarbituric acid, isocarbostyril, 1,2,3,4-tetrahydroisoquinolin, 2-hydroxypyridine, 3,3-dimethylflutarimide, 1,3-dihydroxynapthalene, 1,3-cyclopentanedione, 2-pyrrole amide, 3-pyrrole amide, 1-pyrrole amide and substituted benzamides. Preferable compounds of the invention, having

30   a xanthine core moiety, may include, but are not limited to, compounds having a single epoxide-substituted alkyl side chain (R) at position 1 of the xanthine nucleus.

The inventive compounds may be provided as enantiomeric or diastereomeric mixtures or in resolved or partially resolved forms. Standard procedures are used for resolution of optical isomers. It is contemplated that the different enantiomeric variants (*e.g.*,

35   stereoisomers and chiral forms) of the epoxide-containing compounds will have different drug activities, based upon their differential ability to inhibit PAPH and LPAAT. An optical isomer substantially free of the corresponding enantiomer and/or diastereomers has at least about 85% relevant optical isomer, preferably at least about 95% relevant optical isomer and

especially at least about 99% or higher relevant optical isomer, but most preferably where the amount of other optical forms is undetectable.

The invention further comprises a pharmaceutical composition comprising one or a plurality of inventive compounds and a pharmaceutically acceptable carrier or excipient. The

5   cells to be treated with an inventive compound or inventive pharmaceutical composition may either be contacted with the compound of the invention in *in vitro* culture, in an extracorporeal treatment, or by administering the compound of the invention or pharmaceutical composition thereof to a subject whose cells are to be treated.

Illustrative compounds of the invention include both racemic mixture and R and S

10   enantiomers of the following compounds (designated accordingly as R and S) shown in Table I:

Table I

CT1103	N-(5,6-Oxidohexyl)phthalimide
CT1105	N-(8,9-Oxidononyl)phthalimide
CT1109	N-(10,11-Oxidoundecyl)phthalimide
CT1114	N-(10,11-Oxidoundecyl)homophthalimide
CT1206	1-(5,6-Oxidohexyl)-3-methylbenzoyleneurea
CT1301	N-(5,6-Oxidohexylamido)glutaric acid, methyl ester
CT1409	1-(8,9-Oxidononyl)-3-methyl-7-methylpivaloylxanthine
CT1410	1-(5,6-Oxidononyl)-3-methyl-7-methylpivaloylxanthine
CT1412	1-(11,10-Oxidoundecyl)-3-methyl-7-methylpivaloylxanthine
CT1553	1-(7,8-Oxidooctyl)-3,7-dimethylxanthine
CT1553	1-(7,8-Oxidooctyl)-3,7-dimethylxanthine
CT1555	1-(4,5-Oxidohexyl)-3,7-dimethylxanthine
CT1560	1-(8,9-Oxidononyl)-3,7-dimethylxanthine
CT1565	1-(9,10-Oxidodecyl)-3,7-dimethylxanthine
CT1569	1-(6,7-*trans*-Oxidononyl)-3,7-dimethylxanthine
CT1586	1-(6,7-Oxidoheptyl)-3,7-dimethylxanthine
CT1588	1-(3-(R)-Methyl-7-methyl-(6,7-oxidooctyl)-3,7-dimethylxanthine
CT1593	1-(4,5-Oxidopentyl)-3,7-dimethylxanthine
CT1594	1-(7,8-Oxidoundecyl)-3,7-dimethylxanthine
CT1605	N-(5,6-Oxidohexyl)glutarimide
CT1606	N-(8,9-Oxidononyl)glutarimide
CT1611	N-(10,11Oxidoundecyl)glutarimide
CT1618	N-(10,11-Oxidoundecyl)-2-pieridone
CT1619	N-(5,6-Oxidohexyl)piperidine
CT1804	3-(8,9-Oxidononyl)-1-methyluracil
CT1808	3-(5,6-Oxidohexyl)-1-methyluracil
CT1820	3-(5,6-Oxidoheyl)-1-methyldihydrouracil

CT1822	3-(10,11-Oxidoundecyl)-1-methyldihydrouracil
CT1906	3-(5,6-Oxidohexyl)-1-methylthymine
CT1910	3-(8,9-Oxidononyl)-1-methylthymine
CT1932	3-(11,10-Oxidoundecyl)-1-methylthymine
CT2513	1-(3,4-Oxidobutyl)-3,7-dimethylxanthine
CT2518	1-(11,12-Oxidodecyl)-3,7-dimethylxanthine
CT2541	1-(9,10-Oxidooctadecyl)-3,7-dimethylxanthine
CT2548	1-(4-Methyl-7,8-oxido-8-methylnonyl)-3,7-dimethylxanthine
CT2552	1-(3,7-dimethyl-2,3,6,7-dioxidooctyl)-3,7-dimethylxanthine
CT2562	1-(12,13-Oxidotridecyl)-3,7-dimethylxanthine
CT2563	1-(7,8-cis-Oxidodecyl)-3,7-dimethylxanthine
CT3503	1-(13,14-Oxidotetradecyl)-3,7-dimethylxanthine
CT3516	1-(16,17-Oxidoheptadecyl)-3,7-dimethylxanthine

Uses of the Invention Compounds and Pharmaceutical Formulations

The compounds of the invention provide a mechanism to maintain homeostasis in cells contacted by primary stimuli through mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of the primary stimulus.

5   The foregoing *in vitro* effects give rise to inventive pharmaceutical compositions comprising an effective amount of at least one of the inventive compounds or a pharmaceutically acceptable salt, hydrate or solvate thereof and at least one pharmaceutically acceptable excipient or carrier. Because the inventive compounds, *inter alia*, inhibit cellular signaling, mediated for example by the IL-1 Type I receptor and are IL-1
10   antagonists, the inventive pharmaceutical compositions are useful for: 1) protecting and treating endotoxic shock and sepsis induced by gram positive or negative bacteria; 2) inhibiting, treating or preventing tumor cell growth, such as cancer; 3) stimulating hematopoiesis inhibited by cytoreductive therapies (*e.g.*, chemotherapy or radiotherapy); 4) treating or preventing autoimmune diseases, such as insulin dependent diabetes mellitus
15   (IDDM), arthritis (including rheumatoid arthritis), multiple scherosis, Alzheimers disease, glomerular nephritis, Graves disease, and atheroschlerosis; 5) treating or preventing male pattern baldness by stimulation of hair growth through reversal of an apoptotic process; 6) preventing hair loss caused by cytoreductive therapies; 7) preventing the symptoms of ARDS (acute respiratory distress syndrome) caused by trauma; 8) treating or preventing asthma,
20   inflammatory bowel disease, acute and myelogenous leukemia, transplant rejection, psoriasis, osteoporosis, periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders; and 9) preventing synergistic immunosuppression in GVHD (graft versus host disease).

Excessive or unregulated TNF (tumor necrosis factor) production may play a
25   role in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis,

septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft versus host reaction, allograft rejections, fever, myalgias due to infection such as influenza, cachexia

5   secondary to infection, AIDS or malignancy, AIDS, other viral infections (*e.g.*, CMV, influenza, adenovirus, herpes family), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis. The inventive compounds or pharmaceutically acceptable salts thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human or other mammal, which is

10   exacerbated or signaled 1) through the specific phospholipid-based messenger pathway that amplifies signals within a cell, and 2) by excessive or unregulated production of messenger inflammatory cytokines such as TNF or IL-1. With regard to TNF messenger signaling, there are several disease states in which excessive or unregulated monocyte/macrophage TNF production exacerbates or causes the disease. These include, for example, neurodegenerative

15   diseases such as Alzheimers disease, endotoxemia or toxic shock syndrome (Tracey et al., *Nature* 330:662, 1987 and Hinshaw et al., *Circ. Shock* 30:279, 1990); cachexia (Dezube et al., *Lancet* 355:662, 1990), and adult respiratory distress syndrome (Miller et al., *Lancet* 2(8665):712, 1989). The inventive compounds may be used topically in the treatment of prophylaxis of topical disease states mediated or exacerbated by excessive TNF or IL-1, such

20   as viral infections (herpes or viral conjunctivitis), psoriasis, fungal or yeast infections (ringworm, athletes foot, vaginitis, dandruff, etc.) or other dermatologic hyperproliferative disorders. High TNF levels have been implicated in acute malaria attacks (Grau et al., *N. Engl. J. Med.* 320:1585, 1989), chronic pulmonary inflammatory diseases such as silicosis and asbestosis (Piguet et al., *Nature* 344:245, 1990, and Bissonnette et al., *Inflammation*

25   13:329, 1989), and reperfusion injury (Vedder et al., *Proc. Natl. Acad. Sci. USA* 87:2643, 1990). Therfore, the inventive compounds may preferably be used to stimulate hematopoiesis, prevent and treat septic shock, treat acute and chronic inflammatory disease, treat or prevent an autoimmune disease, treat a fungal or yeast infection, and stimulate hair growth (when applied topically, as confirmed in *in vivo* results on nude mice).

30   The inventive compounds are useful as an adjuvant to inhibit toxic side effects of drugs. These side effects include, for example, side effects of: 1) interleukin-2 (IL-2); 2) cyclosporin A and FK506; and 3) amphotericin B. The inventive compounds also inhibit antigen-induced T cell activation, like cyclosporin or FK506, but, unlike cyclosporin or FK506, do not: 1) prevent generation of NK and LAK cells; 2) suppress IL-2 release from T

35   cells; or 3) suppress IL-8 release.

              Metalloproteases mediate tissue damage such as glomerular diseases of the kidney, joint destruction in arthritis, and lung destruction in emphysema, and play a role in tumor metastases. Three examples of metalloproteases include a 92 kD type V gelatinase induced by TNF, IL-1 and PDGF plus bFGF, a 72 kD type IV collagenase that is usually

constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and IL-1. The inventive compounds can inhibit TNF or IL-1 induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by 100 U/ml of IL-1. Accordingly, the inventive compounds prevent induction of certain metalloproteases induced by IL-1 or TNF and are not involved with constitutively produced proteases (*e.g.*, 72 kD type IV collagenase) involved in normal tissue remodeling.

For example, the compounds of the invention are used in connection with patients undergoing bone marrow transplantation (BMT), regardless of whether the BMT is matched allogeneic, mismatched allogeneic, or autologous. Patients receiving autologous transplants are aided by treatment with compounds of the invention even though they do not necessarily need to be administered immunosuppressive agents, since they do not develop graft-versus-host disease (GVHD). However, the toxic effect of the chemotherapy or radiation therapy used in connection with the disease, in response to which the transplantation has been performed, constitutes a negative stimulus with regard to the patients' cells.

In general, all patients undergoing BMT require doses of chemotherapy with or without total body irradiation that exceed the lethal dose for normal bone marrow recovery. This provides the rationale for using either stored patient marrow or donor marrow to rescue the patient. In general, chemotherapy and radiation are delivered to the patient for 7-10 consecutive days before the new or stored bone marrow is infused. The day on which the marrow is given to the patient is referred to as day 0 of the transplant. Previous days on which the patient received chemo/radiation are designated by negative numbers. Subsequent days are referred to by positive numerals. The median time in which negative responses in BMT recipients occurs is within the first 100 days after transplant. Therefore, statistically, if patients survive through day 100, their chances for continued survival are significantly enhanced. The inventive compounds are able to increase the percentage of patients who survive. The percentage of fatalities within the first 100 days that is considered acceptable is 15-20% for "good risk" patients and 30-40% for "high risk". These fatalities are due to the direct effects of high doses of chemo/radiation. In addition, GVHD contributes to the death rate in allogeneic marrow recipients.

Other indications for which it is useful to administer the compounds of the invention include the presence of a tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, mucositis, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of rhinorrhea, serious drainage, diffuse tissue edema, and generalized pruritus. Other symptoms of chronic allergic response include, as well as the foregoing, dizziness, diarrhea, tissue hyperemia, and lacrimal swelling with localized lymphocyte infiltration. Allergic reactions are also associated with leukotriene release and the distal effects thereof, including asthmatic

symptoms including development of airway obstruction, a decrease in FEV1, changes in vital capacity, and extensive mucus production.

Other suitable subjects for the administration of compounds of the invention, include patients being administered toxic agents for the treatment of tumors, such as

5   chemotherapeutic agents or irradiation therapy, as well as treatment with biological response modifiers such as

IL-2 and tumor suppressing cells such as lymphokine activated killer cells (LAK) and tumor-infiltrating lymphocytes (TIL cells); patients suffering from neoplasias generally, whether or not otherwise treated including acute and chronic myelogenous leukemia, hairy cell

10   leukemia, lymphomas, megakaryocytic leukemia, and the like; disease states caused by bacterial, fungal, protozoal, or viral infection; patients exhibiting unwanted smooth muscle cell proliferation in the form of, for example, restenosis, such as patients undergoing cardiac surgery; patients who are afflicted with autoimmune diseases, thus requiring deactivation of T and B cells, and patients who have neurological disorders.

15   The compounds of the invention further are able to decrease the enhanced levels of a relevant PA and DAG resulting from stimulation of synaptosomes with acetylcholine and/or epinephrine. This suggests that the effects of the compounds of the invention are to both enhance the release of inhibitory neural transmitters such as dopamine, and to modulate the distal "slow current" effects of such neurotransmitters.

20   Thus, the drugs of the invention are also useful to raise the seizure threshold, to stabilize synapses against neurotoxins such as strichnine, to potentiate the effect of anti-Parkinson drugs such as L-dopa, to potentiate the effects of soporific compounds, to relieve motion disorders resulting from administration of tranquilizers, and to diminish or prevent neuron overfiring associated with progressive neural death following cerebral vascular events

25   such as stroke. In addition, the compounds of the invention are useful in the treatment of norepinephrine-deficient depression and depressions associated with the release of endogenous glucocorticoids, to prevent the toxicity to the central nervous system of dexamethasone or methylprednisolone, and to treat chronic pain without addiction to the drug. Further, the compounds of the invention are useful in the treatment of children with

30   learning and attention deficits and generally improve memory in subjects with organic deficits, including Alzheimer's patients.

While dosage values will vary, therapeutic efficacy is achieved when the compounds of the invention are administered to a human subject requiring such treatment as an effective oral, parenteral, or intravenous sublethal dose of about 200 mg to about 5000 mg per day,

35   depending upon the weight of the patient. A particularly preferred regimen for use in treating leukemia is 4-50 mg/kg body weight. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted to the individual's need and to the professional judgment of the person administering or supervising the administration of the inventive compounds.

Coadministration With a P-450 Inhibitor

The coadministration *in vivo* of the compounds of the invention along with an inhibitor of P-450 results in an enhanced effect due to a longer half life of the inventive compounds. This *in vivo* effect is due to inhibition of a degradation pathway for the

5   compounds of the invention. For example, NIH3T3-D5C3 cells can be used to compare effects of an inventive compound alone or in combination with a P-450 inhibitor by comparing transformation phenotype control, incubation with an inventive compound, and coincubation of an inventive compound with the P-450 enzyme inhibitor.

Compounds that inhibit P-450 include, for example, (mg range daily dosage)

10   propranolol (20-100), metaprolol (20-100); verapamil (100-400), diltiazem (100-400), nifedipine (60-100); cimetidine (400-2,400); ciprofloxacin (500-2000), enoxacin (500-2,000), norfloxacin (500-2000), ofloxacin (500-2,000), pefloxacin (500-2,000); erythromycin (100-1,000), troleandomycin (100-1,000); ketoconizole (100-2,000), thiabenzadole (100-1,000); isoniazid (100-1000); mexiletine (100-1,000); and dexamethasone (1-100 mg).

15   For combination therapy, the compounds of the invention and a P-450 inhibitor can be administered individually or in a single composition. A suitable formulation will depend on the nature of the disorder to be treated, the nature of the medicament chosen, and the judgment of the attending physician. In general, the inventive compounds are formulated either for injection or oral administration, although other modes of administration such as

20   transmucosal or transdermal routes may be employed. Suitable formulations for these compounds can be found, for example, in *Remington's Pharmaceutical Sciences* (latest edition), Mack Publishing Company, Easton, PA.

Depending on the inventive compound selected, the level of dosage can be appreciably diminished by coadministration of a P-450 inhibitor, such as a quinolone.

25   Alternatively, a strong synergistic effect may be obtained with such a quinolone.

The invention, illustrated by the following examples, should not be deemed limited by these examples in any way. In these examples PTX means pentoxifylline.

Example 1

This example illustrates a synthesis of N-(5,6-Oxidohexyl)phthalimide (CT1103). 1-

30   bromo-5-hexene (6.52 g, 40 mmol) was added to a potassium phthalimide (7.4 g, 40 mmol) suspension in 50 mL of dimethyl sulfoxide and stirred overnight. After 12 hours of stirring at room temperature, the reaction was poured into a separatory funnel containing 300 mL of water and extracted with dichloromethane (5 X 200 mL). The organic extracts were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous

35   magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel (eluant: 10% acetone/hexane) to yield 9.2 g (100% yield) of an N-(5-Hexenyl)phthalimide (CT1101).

A solution of N-(5-Hexenyl)phthalimide (1.145 g, 5 mmol), prepared as described above, and *m*-chloroperoxybenzoic acid (2.58 g, 7.5 mmol, 50% by wt) in dichloromethane

(30 mL) was stirred for 5 hours. The reaction mixture was diluted with 80 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (20 mL), saturated sodium bicarbonate solution (20 mL), water and brine solutions. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure.
5   The crude product obtained was further purified by flash chromatography over silica gel (using an eluant of 50% hexane and ethyl acetate) to yield 0.918 g (75% yield) of N-(5,6-Oxidohexyl)phthalimide.

Example 2

This example illustrates a synthesis of N-(9,8-Oxidononyl)phthalimide (CT1105). 1-
10   bromo-8-nonene (8.2 g, 40 mmol) was added to a suspension of potassium phthalimide (7.4 g, 40 mmol) in 50 mL of dimethyl sulfoxide and stirred overnight. After 12 hours of stirring at room temperature, the reaction product was poured into a separatory funnel containing 300 mL of water and extracted with dichloromethane (5 X 200 mL). Organic extracts were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous
15   magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel (using an eluant of 10% acetone/hexane) to yield 7.6 g (70.4 % yield) of N-(8-Nonenyl)phthalimide (CT1101).

A solution of N-(8-Nonenyl)phthalimide (1.355 g, 5 mmol), prepared in accordance with the above process, and m-chloroperoxybenzoic acid (2.58 g, 7.5 mmol, 50% by wt) in
20   dichloromethane (30 mL) was stirred for 5 hours. The reaction mixture was diluted with 80 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (20 mL), saturated sodium bicarbonate solution (20 mL), water and brine solutions. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over
25   silica gel (using an eluant of 50% hexane/ethyl acetate), yielding 1.03 g (70% yield) N-(9,8-Oxidononyl)phthalimide.

Example 3

This example illustrates a synthesis of N-(10,11-Oxidoundecyl)phthalimide (CT1109). To a suspension of potassium phthalimide (4.17 g, 22.5 mmol) in
30   dimethylsulfoxide (30 mL) was added 11-undecenyl bromide (available through MTM) (5.0 g, 21.5 mmol) and the reaction mixture stirred for 16 hours at 60°C. The mixture was then poured into water (80 mL) and extracted with ethyl acetate (3 x 70 mL). The combined extracted organic portions were washed with water (3 x 100 mL), dried with magnesium sulfate and evaporated, resulting in a cream-colored solid. Purification by column
35   chromatography (using ethyl acetate/hexane) yielded (5.50g, 86%) N-(10-Undecenyl)phthalimide (CT-1107) as a white solid.

A solution of N-(10-Undecenyl)phthalimide (4.97 g, 16.6 mmol), prepared as discribed above, 4-methylmorpholine-N-oxide (8.62 mL, 60% by wt in water, 50.0 mmol) and potassium osmate dihydrate (58 mg, 0.16 mmol) in 100 mL acetone/water (1:1 by wt)

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was stirred for 16 hours. Water (100 mL) and sodium sulfite (10 g) were added and the resulting solution stirred for an additional hour. The resulting reaction mixture was extracted with dichloromethane (3 x 80 mL) and the organic phase dried using magnesium sulfate and evaporated to obtain 3.93 g (71% yield) of N-(10,11-Dihydroxyundecyl)phthalimide

5   (CT1108).

N-(10,11-Dihydroxyundecyl)phthalimide (2.35 g, 7.10 mmol) was stirred for 3 hours with HBr (6.90 mL of a 30% solution in acetic acid, 21.3 mmol). The mixture was then added over 10 minutes to a solution of water (50 mL), ice (25 g) and NaHCO3 (15 g) and stirred for an additional 30 min. The resulting reaction product was extracted with

10   dichloromethane (3 x 70 mL) and the combined organic phase was dried using magnesium sulfate and evaporated, yielding a residue of N-(10-acetoxy-11-bromoundecyl)phthalimide.

Without further purification, this crude product was treated in methanol (10 mL) with a solution of sodium methoxide (prepared from sodium -- 0.23 g, 10.0 mmol -- and 10 mL methanol). After 60 minutes the reaction mixture containing treated crude product was

15   added to water (30 mL) and extracted with dichloromethane (100 mL, 2 x 50 mL). The extracted organic portions were combined, dried and evaporated, yielding 2.00 g (89% yield) N-(10,11-Oxidoundecyl)phthalimide (CT1109) as a white solid.

Example 4

This example illustrates a synthesis of N-(10,11-Oxidoundecyl)homophthalimide

20   (CT1114). A mixture of homophthalic acid (54.0 g; 0.3 mole) and finely powdered urea (19.82 g; 0.33 mole) were heated to 175-185°C until no more ammonia evolves, evidenced by pH paper. The crude product was refluxed with methanol (500 mL) and homophthalimide isolated by filteration (29g; 60%). Sodium hydride(95%) (576 mg, 24 mmol) was added to a solution of homophthalimide (3.2 g, 20 mmol) in anhydrous

25   dimethylsulfoxide (75 mL). After 20 minutes of stirring, 1-bromoundec-10-ene (5.6 g, 24 mmol) was added. After 16 hours of stirring at room temperature, the reaction mixture was poured into a separatory funnel containing 500 mL of water and extracted with ethyl acetate (3 X 100 mL). The organic extracts were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

30   The crude product obtained was further purified by flash chromatography over silica gel using petroleum ether/5% ethyl acetate eluant to yield 2.2 g (35.5% yield) N-(10-Undecenyl)homophthalimide.

A solution of olefin N-(10-Undecenyl)homophthalimide (1.4 g, 4.5 mmol), and m-chloroperoxybenzoic acid (2.3 g, 6.7 mmol) (50% by wt) in dichloromethane (50 mL) was

35   stirred for 5 hours. The reaction mixture was diluted with 80 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (20 mL), saturated sodium bicarbonate solution (20 mL), water (50 mL) and brine solutions (50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using

75% hexane/ethyl acetate eluant to yield 1.38 g (94% yield) N-(10,11-Oxidoundecyl)homophthalimide.

Example 5

This example illustrates a synthesis of 1-(5,6-Oxidohexyl)-3-methylbenzoyleneurea (CT1206). Sodium metal (0.071 g, 3.1 mmol) was dissolved in methanol (3.1 mL) to prepare a 1.0 molar solution of sodium methoxide. 1-(5-Acetoxy-6-bromohexyl)-3-methylbenzoyleneurea (1.17 g, 2.9 mmol) was dissolved into methanol (25 mL) and added to the sodium methoxide solution over 5 minutes. After stirring for 1 hour, 50 mL of water were added to the solution. The acqueous phase was extracted using three 25 mL aliquots of dichloromethane. The organic phase was dried over sodium sulfate, filtered and the solvent removed under vacuum yielding 0.77 g (97% yield) of white, solid 1-(5,6-Oxidohexyl)-3-methylbenzoyleneurea).

Example 6

This example illustrates a synthesis of 3-Methyl-7-methylpivaloyl-1-(8,9-oxidononyl)xanthine (CT1409). A mixture of 3-methylxanthine (Aldrich, 1.00 g, 6.0 mmol), sodium hydride (145 mg, 6.0 mmol) and dimethyl sulfoxide (20 mL) was stirred until homogeneous (0.5 hours). Chloromethylpivalate (865mL, 904 mg, 6.0 mmol) was added and the reaction stirred for 18 hours. The reaction mixture was poured into water (70 mL) and then extracted with 25% ethanol/dichloromethane (4 X 60 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum to a volume of 40 mL. This solution was cooled in icewater, whereupon a thick white precipitate was formed. The solid was filtered off under suction and dried under vacuum to yield 1.43 g (90% yield) 3-methyl-7-(methylpivaloyl)xanthine (CT1404).

A mixture of 3-methyl-7-(methylpivalyl)xanthine (2.14g, 7.6 mmol) and sodium hydride (183 mg, 7.6 mmol) in dimethyl sulfoxide (30 mL) were stirred for 15 minutes, after which period, 9-bromo-1-nonene (1.56 g, 7.6 mmol) was added. After stirring at ambient temperature for 2 days, the reaction mixture was poured into water (50 mL) and extracted with dichloromethane (3 X 50 mL). The combined organic portions were washed with water (2 X 20 mL) and saturated aqueous sodium chloride solution (30 mL). The solvent was removed under vacuum to give a thick oil. Chromatography (silica, ethyl acetate/20% hexane) of this residue yields 1.46 g (48% yield) of a white, solid, 3-methyl-7-methylpivaloyl-1-(8-nonenyl)xanthine (CT1411).

A mixture of 3-methyl-7-methylpivaloyl-1-(8-nonenyl)xanthine (910 mg, 2.3 mmol), 3-chloroperbenzoic acid (1.16 g of a 50% mixture, 3.4 mmol), and sodium bicarbonate (857 mg, 10 mmol) in dichloromethane (15 ml) and water (10 mL) was stirred for 18 hours at ambient temperature. A saturated aqueous solution of sodium bisulfite was added (15 mL) and stirring is continued for 30 minutes. The layers are separated and the aqueous layer extracted with dichloromethane (3 X 30 mL). The combined organic layers were combined and washed with saturated aqueous sodium bicarbonate solution (20 mL), water (20 mL) and

saturated aqueous sodium chloride solution (20 mL) and then dried over sodium sulfate.
Solvent was evaporated under vacuum. Chromotography of this residue using silica and a
dichloromethane/5% ethanol eluant yielded 660 mg (68% yield) 3-methyl-7-methylpivaloyl-
1-(8,9-oxidononyl)xanthine (CT1409).

5   **Example 7**

This example illustrates a synthesis of 1-(8,9-Oxidohexyl)-3-methyl-7-
methylpivaloylxanthine (CT1410). A mixture of 3-methylxanthine (Aldrich, 1.00 g, 6.0
mmol), sodium hydride (145 mg, 6.0 mmol) and dimethyl sulfoxide (20 mL) was stirred
until homogeneous (0.5 hours). Chloromethylpivalate (865mL, 904 mg, 6.0 mmol) was
10   added and the reaction stirred for 18 hours. The reaction mixture was poured into water (70
mL) and then extracted with 25% ethanol/dichloromethane (4 X 60 mL). The combined
organic extracts were dried over sodium sulfate and evaporated under vacuum to a volume of
40 mL. This solution was cooled in icewater, whereupon a thick white precipitate formed.
The solid was filtered off under suction and dried under vacuum to yield 1.43 g (90% yield)
15   3-methyl-7-(methylpivaloyl)xanthine (CT1404).

Sodium hydride (86 mg, 3.6 mmol) was added to a stirring solution of 3-methyl-7-
(methylpivaloyl)xanthine CT1404 (1.00 g, 3.6 mmol) in dimethyl sulfoxide (25 mL). After
15 minutes, 6-bromo-1-hexene (589 mg, 3.6 mmol) was added and stirring continued for 72
hours. The reaction mixture was then poured into water (70 mL) and extracted with
20   dichloromethane (2 X 100 mL) and 20% ethanol/dichloromethane (1 X 100 mL). The
combined organic layers were washed with saturated aqueous sodium chloride solution (50
mL) and dried over magnesium sulfate. The solvent was evaporated under vacuum to give a
thick oil. Chromotograpy of the resulting thick oil using silica and ethyl acetate yielded 870
mg (67% yield) 1-(5-hexenyl)-3-methyl-7-(methylpivaloyl)xanthine (CT1441)

25   A mixture of 1-(5-hexenyl)-3-methyl-7-(methylpivaloyl)xanthine (440 mg, 1.2
mmol) and m-chloroperoxybenzoic acid (828 mg of 50% m-chloroperoxybenzoic by wt, 2.4
mmol) in dichloromethane (10 mL) and sodium bicarbonate (807 mg, 9.2 mmol) in water (10
mL) was stirred for 20 hours. Sodium metabisulfite (1.0 g, 5.3 mmol) was added. After 30
minutes, the reaction mixture was extracted with dichloromethane (3 x 10 mL). The
30   combined organic portions were washed with saturated aqueous sodium bicarbonate solution
(10 mL) and the solvent was evaporated under vacuum. Chromatography of the residue on
silica using 10% pet ether/ethyl acetate eluant yielded 146 mg (32% yield) 1-methyl-7-
(methylpivaloyl)-3-(5,6-oxidohexyl)xanthine (CT1410).

Example 8

35   This example illustrates a synthesis of 1-(11,10-Oxidoundecanyl)-3-methyl-7-
methylpivalylxanthine (CT1412). A mixture of 3-methylxanthine (Aldrich, 1.00 g, 6.0
mmol), sodium hydride (145 mg, 6.0 mmol) and dimethyl sulfoxide (20 mL) was stirred
until homogeneous (0.5 hours). Chloromethylpivalate (865mL, 904 mg, 6.0 mmol) was
added and the reaction stirred for 18 hours. The reaction mixture was poured into water (70

mL) and then extracted with 25% ethanol/dichloromethane (4 X 60 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum to a volume of 40 mL. This solution was cooled in icewater, whereupon a thick white precipitate formed. The solid was filtered off under suction and dried under vacuum to yield 1.43 g (90% yield)
5   3-methyl-7-(methylpivaloyl)xanthine (CT1404).

Sodium hydride (76.8 mg, 3.2 mmol) was added to a solution of 3-methyl-7-pivaloylxanthine (0.84 g; 3 mmol) and 11-bromoundec-10-ene (0.745 g; 3.2 mmol) in 15 mL of dimethyl sulfoxide and stirred overnight. After 12hours of stirring at room temperature, the reaction was poured into a separatory funnel containing 30 mL of water and extracted
10   with dichloromethane (5 X 50 mL). The organic extracts were combined, washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 50% hexane/ethyl acetate eluant to yield 1.05 g (73.8% yield) 1-(10-undecenyl)-7-methylpivaloyl-3-methylxanthine
15   (CT1403).

A solution of 1-(10-undecenyl)-7-methylpivaloyl-3-methylxanthine (0.60 g; 1.39 mmol), and m-chloroperoxybenzoic acid (0.359 g; 2 mmol, 50% by wt) in dichloromethane (10 mL) was stirred for 5 hours. The reaction mixture was diluted with 40 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution(20
20   mL), saturated sodium bicarbonate solution (20 mL), water and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 50% hexane and ethyl acetate eluant, yielding 0.443g (72% yield) 1-(11,10-Oxidoundecanyl)-3-methyl-7-methylpivalylxanthine.

25   **Example 9**

This example illustrates a synthesis of 1-(11,10-Oxidoundecanyl)-3-methylxanthine (CT1413). A solution of 1-(11,10-Oxidoundecanyl)-3-methyl-7-methylpivalylxanthine (CT1412), prepared as described above (104 mg; 0.23 mmol), was added to a solution of sodium methoxide (15.1 mg; 0.28 mmol) in 3 mL of methanol and stirred for 4 hours. The
30   reaction mixture was quenched with saturated ammonium chloride solution (5 mL) and extracted with 20% ethanol/dichloromethane (3x30 mL). The combined organic extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 10% methanol/ethyl acetate eluant to yield 75 mg (96.7%) of (11,10-Oxidoundecanyl)-3-
35   methylxanthine (CT1413).

Example 10

This example illustrates a synthesis of 7-(11,10-Oxidondecyl)-1,3-dimethylxanthine (CT-1423). Sodium hydride(95%) (0.575 g, 24 mmol) was added to a solution of theophylline (3.6 g, 20 mmol) in dimethylsulfoxide (100 mL). After 20 minutes of stirring,

1-bromoundec-10-ene (4.66 g, 20 mmol) was added and stirred for 12 hours at room temperature. The reaction mixture was then poured into a separatory funnel containing water (300 mL) and extracted with dichloromethane (5 X 100 mL). The organic extracts were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous

5   magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 50% hexane/ethyl acetate eluant, yielding 6.26 g (94% yield) of 7-(10-undecenyl)-1,3-dimethylxanthine (CT1420).

A solution of 7-(10-undecenyl)-1,3-dimethylxanthine (4.98 g, 15 mmol) and m-chloroperoxybenzoic acid (7.704 g; 22.5 mmol) (50% by wt) in dichloromethane (100 mL)

10   was stirred for 5 hours. The reaction mixture was diluted with 80 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (100 mL), saturated sodium bicarbonate solution (100 mL), water (100 mL) and brine solution (100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over

15   silica gel using 50% petroleum ether/ethyl acetate eluant to yield 3.13 g (60% yield) of 7-(11,10-Oxidondecyl)-1,3-dimethylxanthine.

Example 11

This example illustrates a synthesis of 7-(11,10-Oxidondecyl)-1-methyl-2,4-dioxotetrahydropteridine (CT1426). 1-Methyl-4,5-diaminouracil (13.6 g; 59.4 mole) was

20   suspended in water (150 mL) and converted to its hydrochloride by drop-wise addition of concentrated hydrochloric acid unitl the solution is strongly acidic. Glyoxan sodiumbisulphite (20.4 g; 71.8 mmol) was then added and the reaction mixture refluxed for 30 minutes. The reaction mixture was cooled to room temperature and the precipitated 1-methyl-2,4-dioxotetrahydropteridine isolated by filteration, yielding 6.5 g (62%). Sodium

25   hydride (95%,) (0.575 g, 24 mmol) was added to a solution of 1-methyl-2,4-dioxotetrahydropteridine (3.56 g, 20 mmol) in dimethylsulfoxide (100 mL). After 20 minutes of stirring, 1-bromoundec-10-ene (4.66 g, 20 mmol) was added and stirred for 12 hours at room temperature. The reaction mixture was then poured into a separatory funnel containing water (300 mL) and extracted with ethyl acetate (5 X 100 mL). The organic extracts were

30   combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 50% hexane/ethyl acetate eluant to yield 5 g (94% yield) of 3-(10-undecenyl)-1-methyl-2,4-dioxotetrahydropteridine (CT1421). A solution of 3-(10-undecenyl)-1-methyl-2,4-dioxotetrahydropteridine (3.3 g, 10 mmol) and m-

35   chloroperoxybenzoic acid (5.13 g; 15 mmol) (50% by wt) in dichloromethane (50 mL) was stirred for 5 hours. The reaction mixture was diluted with 40 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (20 mL), saturated sodium bicarbonate solution (20 mL), water (30 mL) and brine solutions (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The

crude product obtained was further purified by flash chromatography over silica gel using 40% petroleum ether/ethyl acetate eluant to yield 2.61 g (75% yield) of 7-(11,10-Oxidondecyl)-1-methyl-2,4-dioxotetrahydropteridine.

Example 12

5   This example illustrates a synthesis of 1-Methyl-3-(5,6-oxidohexyl)xanthine (CT1439). A solution of 1-methyl-7-(methylpivaloyl)-3-(5,6-oxidohexyl)xanthine, prepared as described above, (120 mg, 0.3 mmol) in methanol (5 mL) was treated with a 1 M methanol solution of sodium methoxide (0.33 mL). After 15 minutes of stirring, water (5 mL) was added and the reaction product was extracted with 25% ethanol/dichloromethane (4

10   X 25 mL). The aqueous layer was evaporated under vacuum leaving a solid residue which is subsequently washed with dichloromethane (4 X 20 mL). The combined organic washings were evaporated under vacuum to a give a solid, yellowish residue. Chromatography of the residue using silica and 50% ethyl acetate/methanol yields 55 mg (69% yield) of solid 1-methyl-3-(5,6-oxidohexyl)xanthine.

15   **Example 13**

This example illustrates a synthesis of 1-(6,7-*cis*-Oxidononyl)-3,7-dimethylxanthine (CT-1509). A mixture of *cis*-6-nonen-1-ol (TCI, 3.00 g, 21.1 mmol) and methanesulfonyl chloride (1.6 mL, 2.4 g, 21 mmol) in dichloromethane (100 mL) at 0°C was treated with triethylamine (4.4 mL, 3.2 g, 32 mmol). After 1 hour the ice bath was allowed to melt.

20   After reaching ambient temperature, the reaction was poured into a separatory funnel containing water (50 mL) and dichloromethane (50 mL). The layers were separated and the aqueous layer washed with dichloromethane (2 X 50 mL). The combined organic layers were dried over sodium sulfate, and solvent removed to yield 4.14 g, 18.8 mmol (89% yield) 6-*cis*-nonene-1-methanesulfonate as a yellow oil.

25   Theobromine (3.36 g, 18.8 mmol) and sodium hydride (451 mg, 18.8 mmol) in dimethylsulfoxide (40 mL) was stirred for 40 minutes after which time the mesylate (4.14 g, 18.8 mmol) was added. The reaction was stirred at 25°C for 3 days, then heated at 80°C for 1 hour, and cooled. The reaction mixture was poured into water (100 mL) and extracted with dichloromethane (3 X 60 mL). The combined organic layers were washed with saturated

30   aqueous salt solution (2 X 50 mL) and dried over sodium sulfate. The solvent was removed. Chromotagraphy using silica and ethyl acetate of the residue yields 4.54 g (79% yield) 1-(6-*cis*--nonenyl)-3,7-dimethylxanthine (CT1508).

A mixture of 1-(6-*cis*-nonenyl)-3,7-dimethylxanthine, prepared as described above, in dichloromethane (10 mL) was stirred with sodium bicarbonate (2.62 g, 31 mmol) in water

35   (20 mL) and 4-chloroperoxybenzoic acid (2.0 g, or 4.0 g of a 50% mixture) for 15 hours. Sodium sulfite (1.82 g, 14.5 mmol) was added, the mixture added to water (50 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with water (40 mL) and saturated aqueous salt solution (40 mL). The solvent was removed to yield a yellow oily residue which was subsequently isolated using silica and ethyl acetate

chromatography, yielding 520 mg (42% yield) of a white, solid 1-(6,7-*cis*-oxidononyl)-3,7-dimethylxanthine.

Example 14

This example illustrates a synthesis of 1-(5,6-Oxidohexyl)-3,7-dimethylxanthine

5   (CT1541). To a mixture of bromohexene (10.7 g, 66 mmol, Aldrich) and sodium hydride (1.58 g, 66 mmol) in dimethylsulfoxide (100 mL) was added theobromine (11.9 g, 66 mmol, available from Sigma) and stirred for 43 hours. The solution was treated with water (200 mL) and extracted with dichloromethane (3 X 80 mL). The combined extracts were washed with water (3 X 100 mL), dried over magnesium sulfate, and then the solvent evaporated

10   under vacuum to yield 17 g (65 mmol, 98% yield) of a white powder, 1-(5-Hexenyl)-3,7-dimethylxanthine (CT1539).

To a mixture of 1-(5-Hexenyl)-3,7-dimethylxanthine (1.07 g, 4.1 mmol) and *N*-methylmorpholine-*N*-oxide (1.44 g, 12.3 mmol) in water (20 mL) and acetone (10 mL) was added 2.5% osmium tetraoxide in *t*-butanol (6 drops). After stirring for 48 hours, the

15   mixture was treated with 20% aqueous sodium dithionite solution (20 mL). After 2 minutes, the mixture is extracted with 25% ethanol-dichloromethane solution (3 X 30 mL). The combined extracts were dried over magnesium sulfate and the solvents were evaporated under vacuum, yielding 750 mg, 2.53 mmol (62% yield) 1-(5,6-dihydroxyhexyl)-3,7-dimethylxanthine (CT1502) as a white powder.

20   To 1-(5,6-dihydroxyhexyl)-3,7-dimethylxanthine 1.0 g, 3.38mmol) was added 30% hydrogen bromide-acetic acid (3.4 mL) over 30 seconds and then stirred for 2.5 hours until all of the solid dissolved. The solution was poured carefully over a mixture of sodium bicarbonate (12 g) and ice water (50 mL). After carbon dioxide evolution had subsided, the mixture was extracted with dichloromethane (3 X 25 mL). The combined extracts were dried

25   over magnesium sulfate and the solvent evaporated under vacuum, yielding 1.3 g (3.24 mmol, 96%) 1-(5-Acetoxy-6-bromohexyl)-3,7-dimethylxanthine as a viscous oil, dissolved in methanol (5 mL). A 1*M* sodium methoxide in methanol solution (3.9 mL) was added over 30 seconds. After stirring for 20 minutes, the solution was reated with water (20 mL) and then extracted with dichloromethane (3 X 15 mL). The combined extracts were dried over

30   magnesium sulfate and the solvents were evaporated under vacuum to yield 900 mg (3.24 mmol, 100% yield) 1-(5,6-Oxidohexyl)-3,7-dimethylxanthine as white crystals.

Example 15

This example illustrates a synthesis of 1-(8,9-Oxidooctyl)-3,7-dimethylxanthine (CT1553). To a suspension of sodium hydride (580 mg, 24.2 mmol) in dimethylsulfoxide

35   (100 mL) was added theobromine (3.96 g, 22.0 mmol). After 30 minutes, 8-bromo-1-octene (3.96 g, 22 mmol) was added and the reaction stirred 16 hours at 25°C. The mixture was then poured into water (200 mL) and extracted with dichloromethane (3 X 50 mL). The combined organic portions were washed with brine (50 mL) and dried over sodium sulfate.

The solvent was evaporated under vacuum to yield 6.22 g (97% yield) of thick white oil, 1-(7-octenyl)-3,7-methylxanthine (CT1535) which solidified upon standing.

A solution of 1-(7-octenyl)-3,7-dimethylxanthine (1.00 g, 4.5 mmol), 4-methylmorpholine-N oxide (553 mg, 4.7 mmol), and a 2.5% solution of osmium tetroxide in t-butanol (3 drops) in acetone (25 mL) and water (20 mL) was stirred for 4 days. After addition of a saturated aqueous solution of sodium hydrosulfite (10 mL) and 30 minutes of continued stirring, the reaction mixture was added to water (50 mL) and extracted with 20% ethanol/dichloromethane (3 X 50 mL). Evaporation of the solvent under vacuum yielded an off-white residue. The residue was recrystallized in ethanol, yielding 726 mg (63% yield) 1-(7,8-dihydroxyoctyl)-3,7-dimethylxanthine (CT1538) as a white solid.

A mixture of 1-(7,8-dihydroxyoctyl)-3,7-dimethylxanthine, prepared as described above, (2.11g, 6 mmol) was stirred with a 30% solution of hydrogen bromide in acetic acid (3.58 mL, 18 mmol) for 90 minutes. The mixture was then added to a flask containing aqueous sodium bicarbonate solution (4 g in 50 mL) and dichloromethane (30 mL). After 10 minutes of vigorous stirring the layers were separated and the aqueous portion was washed with dichloromethane (2 X 50 mL). The combined organic portions were dried over sodium sulfate and the solvent was evaporated under vacuum, yielding 2.51 g (94%) 1-(7-acetoxy-8-bromooctyl)-3,7-dimethylxanthine (CT1514) as a yellow oil.

A solution of 1-(7-acetoxy-8-bromooctyl)-3,7-dimethylxanthine in methanol (10 mL) was treated with a 1 M solution of sodium methoxide (1.4 mL). After 30 minutes, the reaction was added to water (20 mL) and extracted with dichloromethane (2 X 30 mL). Combined organic portions are dried to give an off-white residue, recrystallized in dichloromethane/petroleum ether, yielding 1.42 g (75% yield) 1-(8,9-oxidooctyl)-3,7-dimethylxanthine (CT1553).

Example 16

This example illustrates a synthesis of 1-(4,5-Oxohexyl)-3,7-dimethylxanthine (CT1555). To a solution of 4-hexen-1-ol (1.22 g, 12.2 mmol) and methanesulfonyl chloride (1.04 mL, 13.4 mmol) in dichloromethane (15 mL), cooled in an ice bath, was added triethylamine (2.55 mL, 18.3 mmol) dropwise. After 5 minutes, the cooling bath was removed and the mixture stirred for an additional 45 minutes and then treated with saturated aqueous sodium bicarbonate solution (25 mL). The layers were separated and the aqueous layer extracted with dichloromethane (20 mL). The combined organic layers were dried over magnesium sulfate and the solvents evaporated under vacuum, yielding 1-methanesulfonyloxy-4-hexene as a viscous oil.

A mixture of theobromine (2.16 g, 12 mmol) and sodium hydride (288 mg, 12 mequivalents) in dimethylsufoxide (10 mL) was stirred for 30 minutes and then a solution of 1-methansulfonyloxy-4-hexene in dimethylsulfoxide (10 mL) was added. After 84 hours of stirring, water (70 mL) is added and the mixture extracted with ether (3 x 50 mL). The combined extracts were washed with water (50 mL) and dried over magnesium sulfate. The

solvent was then evaporated under vacuum. The residue was purified by flash
chromatography (22 g silica gel using an ethyl acetate eluant, 500 mL), yielding 2.1 g (67%)
1-(4-hexenyl)-3,7-dimethylxanthine. To a solution of 1-(4-hexenyl)-3,7-dimethylxanthine (270
mg, 1.03 mmol) in dichloromethane (10 mL) was added saturated aqueous sodium bicarbonate

5   solution (10 mL), followed by a solution of 50-60% 3-chloroperoxybenzoic acid (889 mg,
2.58 mmol) in dichloromethane (5 mL) over 1 minute. After 20 hours of stirring, 20%
aqueous sodium metabisulfite solution (15 mL) was added over 1 minute. The mixture was
then extracted with dichloromethane (3 x 15 mL). The combined extracts were washed with
saturated aqueous sodium bicarbonate solution (3 x 20 mL) and dried over magnesium sulfate.

10   The sovent was evaporated under vacuum. The residue was purified by flash chromatography
using 14 g of silica gel and eluting with ethyl acetate (100 ml) followed by 8% methanol-
dichloromethane (60 mL), yielding 80 mg (28% yield) of 1-(4,5-oxohexyl)-3,7-
dimethylxanthine as a white powder.

Example 17

15   This example illustrates a synthesis of 1-(8,9-Oxidononyl)-3,7-dimethylxanthine
(CT1560). A mixture of theobromine (17.64 g, 98 mmol) and sodium hydride (2.35 g, 98
mmol) in dimethylsulfoxide (250 mL) was stirred for 15 minutes. After addition of 9-bromo-
1-nonene (Alfebro, 20.0 g, 98 mmol) stirring was continued at ambient temperature for 3
days. The reaction mixture was then poured into water (300 mL) and extracted with

20   dichloromethane (4 X 200 mL). The combined organic layers are washed with saturated
aqueous salt solution (2 X 150 mL) and dried over sodium sulfate. The solvent was
evaporated under vacuum to give a thick oil. After cooling a solution of the oil in a minimum
of dichloromethane and ether, 1-(8-nonenyl)-3,7-dimethylxanthine (CT1550) (24.34 g, 77.5
mmol, 99% yield) formed as white crystals .

25   A solution of 1-(8-nonenyl)-3,7-dimethylxanthine (810 mg, 2.7 mmol), 4-
methylmorpholine-N- oxide (340 mg, 2.9 mmol) and 2.5% oxmium tetroxide in t-butanol (3
drops) in acetone (20 mL) and water (20 mL) was stirred for 24 hours. Saturated aqueous
sodium dithionite solution (5 mL) was added. After stirring for 15 minutes, the reaction was
extracted with 25% ethanol-dichloromethane (4 X 50 mL). The combined organic portions

30   were dried over sodium sulfate, and the solvents were evaporated under vacuum. The solid
residue was recrystallized (ethanol-chloroform), yielding 490 mg (54%) 1-(8,9-
dihydroxynonyl)-3,7-dimethylxanthine (CT1561).

A mixture of 1-(8,9-dihydroxynonyl)-3,7-dimethylxanthine and 30% hydrogen bromide
in acetic acid (0.8 mL, 3.90 mmol) was stirred for 90 minutes. The solution was poured into a

35   mixture of water (10 mL), sodioum bicarbonate (1.35 g, and dichloromethane (10 mL). After
10 minutes of vigorous stiring, the layers were separated and the aqueous portion extracted
with dichloromethane (3 X 15 mL). The combined organic phases were dried over sodium
sulfate and the solvent evaporated under vacuum, yielding 550 mg (96%) 1-(8-acetoxy-9-
bromononyl)-3,7-dimethylxanthine as a yellow oil. Without further purification, the oil was

dissoved in methanol (5 mL) and then a 1 M solution of sodium methoxide in methanol (1.4 mL) was added. After 30 minutes, the reaction mixture was poured into water (30 mL) and was extracted with dichloromethanone (3 X 40 mL). The combined organic portions were dried over sodium sulfate and the solvents evaporated under vacuum. The solid residue was

5   recrystallized (dichloromethane-petroleum ether) to yield 380 mg (91% yield) 1-(8,9-oxidononyl)-3,7-dimethylxanthine (CT1560).

Example 18

This example illustrates a synthesis of 1-(9,10-Oxidodecyl)-3,7-dimethylxanthine (CT1565). To a solution of 9-decene-1-ol (Aldrich, 3.00 g, 19.2 mmol) in dichloromethane

10 (100 mL) at 0°C was added methanesulfonyl chloride (2.20 g, 1.5 mL, 19.2 mmol), followed by triethylamine (2.91 g, 28.8 mmol). After stirring for 15 minutes at 0°C, the reaction was allowed to warm to room temperature. After 2 hours, the reaction mixture was poured into water (100 mL) and extracted with dichloromethane (3 X 60 mL). The combined organic portions were dried over sodium sulfate and the solvent was evaporated under vacuum

15 yielding 4.52 g (100%) mesylate as a yellow oil. The mesylate was used without further purification.

To a suspension of sodium hydride (461 mg, 19.2 mmol) in dimethylsulfoxide (30 mL) was added theobromine (3.45 g, 19.2 mmol). After 15 minutes, the 9-decenylmesylate (2.25 g, 11 mmol) was added and the reaction stirred 18 hours at 25°C, then at 100°C for 40

20 minutes. The mixture was then poured into water (100 mL) and extracted with dichloromethane (3 X 50 mL). The combined organic portions were washed with saturated salt solution (60 mL) and dried over magnesium sulfate. The solvent was evaporated under vacuum to give a white solid residue. Recrystallization in ether yields 3.40 g (56% yield) 1-(9-decenyl)-3,7-dimethylxanthine (CT1563).

25 A solution of 1-(9-decenyl)-3,7-dimethylxanthine (3.2 g, 10.1 mmol), 4-methylmorpholine-N-oxide (1.41 g, 12 mmol) and a 2.5% solution in t-butanol of osmium tetroxide (3 drops) in acetone (40 mL) and water (10 mL) was stirred for 24 hours. Following addition of 5 mL of a saturated solution of sodium dithionite and an additional 15 minutes of stirring, the reaction product was extracted with 25% ethanol/dichloromethane (4 X 50 mL).

30 The combined organic portions were dried over sodium sulfate. The solvents were evaporated to a give a white solid residue. Upon recrystallization of the residue in ethanol, 3.30 g (93% yield) 1-(9,10-dihydroxydecyl)-3,7-dimethylxanthine (CT1564) were obtained.

A mixture of 1-(5,6-dihydroxydecyl)-3,7-dimethylxanthine (2.11g, 6 mmol) and a 30% solution of hydrogen bromide in acetic acid (3.58 mL, 18 mmol) was stirred for 90

35 minutes. The mixture was then added to a flask containing aqueous sodium bicarbonate solution (5 g in 40 mL) and dichloromethane (50 mL). After 10 minutes of vigorous stirring, the layers were separated and the aqueous portion extracted with dichloromethane (2 X 50 mL). The combined organic phases were dried over sodium sulfate. The solvent was evaporated, yielding 2.72 g (100%) 1-(9-acetoxy-10-bromodecyl)-3,7-dimethylxanthine as a

yellow oil. Without further purification, the oil was taken up in methanol (30 mL) and treated with a 1 M solution of sodium methoxide (6 mL). After 30 minutes, the reaction mixture was added to water (30 mL) and extracted with dichloromethane (3 X 50 mL). The organic portions were combined and dried over sodium sulfate to give an off-white solid

5   residue. Recrystalization in dichloromethane/petroleum ether yields 380 mg (91% yield) 1-(9,10-oxidodecyl)-3,7-dimethylxanthine.

Example 19

      This example illustrates a synthesis of 3,7-dimethyl-1-(6,7-*trans*-oxidononyl)xanthine (CT-1569). A mixture of 6-*cis*-nonen-1-ol (TCI, 990 mg, 7.0 mmol) and thiophenol (60 mg)

10   was heated at 105-110°C under argon for 4 hours to give 6-nonen-1-ol 872 mg, 88% yield) with a 4:1 *trans:cis* isomer ratio. Without further purification, the mixture was stirred with methanesulfonyl chloride (694 mg, 6.1 mmol) in dichloromethane (20 mL) at 0°C. Triethylamine (925 mg, 9.2 mg) was added dropwise and stirring continued for 1 hour. The reaction mixture was added to an aqueous saturated solution of sodium bicarbonate (10 mL)

15   and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with a 5% solution of hydrogen chloride (10 mL), water (10 mL), and an aqueous saturated solution of sodium chloride (10 mL) and then dried over sodium sulfate. The solvent was removed under vacuum to give the mesylate, which was used in the next step without purification.

20   A mixture of the mesylate, sodium theobromine (1.21 g, 6.0 mmol) was stirred in dimethylsulfoxide (10 mL) for 24 hours. The reaction mixture was poured into water (10 mL) and extracted with dichloromethane (3 X 25 mL). The combined organic extracts were washed with water (15 mL) and aqueous saturated salt solution (15 mL). After removing the solvent under vacuum, the residue was purified by silica/ethyl acetate chromotography,

25   yielding 827 mg (67% yield) 1-(6-*trans*-noneyl)-3,7-dimethylxanthine (CT2512), 20% being contaminated with the *cis* isomer.

      1-(6-*trans*-noneyl)-3,7-dimethylxanthine (110 mg, 0.4 mmol), *m*-chloroperbenzoic acid (75 mg, 0.4 mmol), and sodium bicarbonate (150 mg, 1.8 mmol) were stirred in dichloromethane (6 ml) and water (5 mL) for 5 hours at room temperature. A saturated

30   solution of sodium bisulfite was added (10 mL). The layers were separated and the aqueous layer washed with dichloromethane (2 X 20 mL). The organic layers were combined and washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (15 mL), and dried over sodium sulfate. The solvent was evaporated and the residue recrystallized in ether, yielding 70 mg (54% yield) of 1-(6,7-Oxidoheptyl)-3,7-dimethylxanthine.

35   ### Example 20

      This example illustrates a synthesis of 1-(6,7-Oxidoheptyl)-3,7-dimethylxanthine (CT-1586). To a solution of 6-hepten-1-ol (6.00 g, 52.6 mmol) in dichloromethane (120 mL) at 0°C was added methanesulfonyl chloride (6.07 g, 4.0 mL , 53.0 mmol), followed by triethylamine (7.79 g, 77.0 mmol). After stirring for 10 minutes at 0°C, the reaction was

allowed to warm to 25°C and then stirred for 2 hours. The reaction was poured into water (100 mL) and extracted with dichloromethane (2 x 100 mL). The organic portions were combined, dried over magnesium sulfate, and evaporated to give the 7-methanesulfonyl-1-heptene as a yellow oil (9.30 g, 93%), which was used without further purification.

To a suspension of sodium theobromine (9.05 g, 50.0 mmol) in dimethylsulfoxide (90 mL) was added 7-methanesulfonyl-1-heptene (9.30 g, 48.2 mmol). The reaction was stirred for 16 hours at 60°C. The mixture was then poured into water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic portions were combined, dried, and evaporated to give an orange solid. Chromatography (silica, ethyl acetate/hexane) yielded 6.50 g (47% yield) 1-(6-Heptenyl)-3,7-dimethylxanthine (CT1534) as a white solid.

A solution of 1-4(6-Heptenyl)-3,7-dimethylxanthine (6.00 g, 21.7 mmol), 4-methylmorpholine-N-oxide (6.82 g, 58.0 mmol) and potassium osmate dihydrate (70 mg, 0.19 mmol) in acetone/water 1:2 (120 mL) was stirred for 16 hours. Water (100 mL) and sodium sulfite (5 g) were added and the reaction mixture stirred for 1 hour. The reaction mixture was extracted with 25% ethanol/dichloromethane (3 x 120 mL), dried over magnesium sulfate and the solvent evaporated to obtain a cream solid. Recrystallization of the solid from hot methanol/ethyl acetate 1:1 yielded 6.45 g (96% yield) 1-(6,7-Dihydroxyheptyl)-3,7-dimethylxanthine (CT1585) as a white solid.

1-(6,7-Dihydroxyheptyl)-theobromine (4.00 g, 12.9 mmol) was stirred with hydrogen bromide (12.53 g of a 30% solution in acetic acid, 38.7 mmol) for 2 hours. The mixture was then added over 10 minutes to water (50 mL), ice (50 g) and sodium bicarbonate (30 g) and stirred for 30 minutes. The reaction mixture was extracted with dichloromethane (3 x 100 mL). A combined organic phase was dried over magnesium sulfate and the solvent was evaporated to obtain a residue (4.90 g, 91% yield) of 1-(6-acetoxy-7-bromoheptyl)-3,7-dimethylxanthine.

Without further purification, this crude product was taken up in methanol (10 mL) and treated with a solution of sodium methoxide (prepared from sodium (0.285 g, 12.4 mmol) and 20 mL methanol). After 60 minutes the reaction was added to water (50 mL) and extracted with dichloromethane (3 x 50 mL). The organic portions were combined and dried to give an off-white solid. Recrystalization in dichloromethane/petroleum ether yielded 3.30 mg (96% yield) of 1-(6,7-Oxidoheptyl)-3,7-dimethylxanthine.

Example 21

This example illustrates a synthesis of 1-(3-(R)-methyl-7-methyl-6,7-oxidooctyl)-3,7-dimethylxanthine (CT1588R). Sodium hydride(95%) (631 mg, 25 mmol) was added to a solution of theobromine (4.14g, 23 mmol) in dimethylsulfoxide (75 mL). After 20 minutes of stirring, (R)(-)Citronellyl bromide (5.0 g, 22.8 mmol) was added. After 16 hours of stirring at room temperature, the reaction was poured into a separatory funnel containing 500 mL of water and extracted with dichloromethane (3 X 100 mL). The organic extracts were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The crude product obtained
was further purified by flash chromatography over silica gel using 30% petroleum ether/ethyl
acetate eluant, yielding 5.9 g (81.5% yield) 1-(3-(R)-methyl-7-methyloct-6-enyl)-3,7-
dimethylxanthine (CT596R) as a yellowish oil. A solution of 1-(3-(R)-methyl-7-methyloct-
5   6-enyl)-3,7-dimethylxanthine (318 mg, 1 mmol) and m-chloroperoxybenzoic acid (0.52 g;
1.5 mmol) (50% by wt) in dichloromethane (7 mL) was stirred for 5 hours. The reaction
mixture was diluted with 40 mL of dichloromethane and washed successively with 20%
aqueous sodium sulphite solution (10 mL), saturated sodium bicarbonate solution (10 mL),
water and brine solutions. The organic layer was dried over anhydrous magnesium sulfate
10   and concentrated under reduced pressure. The crude product obtained was further purified
by flash chromatography over silica gel using 5% petroleum ether/ethyl acetate eluant,
yielding 0.253 g (76% yield) of 1-(3-(R)-methyl-7-methyl-6,7-oxidooctyl)-3,7-
dimethylxanthine.

Example 22

15   This example illustrates a synthesis of 1-(3-(S)-methyl-7-methyl-6,7-oxidooctyl)-3,7-
dimethylxanthine (CT1588S). Sodium hydride (95%) (631 mg, 25 mmol) was added to a
solution of theobromine (4.14g, 23 mmol) in dimethylsulfoxide (75 mL). After 20 minutes
of stirring, (S)(-)Citronellyl bromide (5.0 g, 22.8mmol) was added. After 16 hours of
stirring at room temperature, the reaction mixture was poured into a separatory funnel
20   containing 500 mL water and extracted with dichloromethane (3 X 100 mL). The organic
portions were combined, washed with water (100 mL) and brine (100 mL), dried over
anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product
obtained was further purified by flash chromatography over silica gel using 30% petroleum
ether/ethyl acetate eluant to yield 5.7 g (80% yield) 1-(3-(S)-methyl-7-methyloct-6-enyl)-3,7-
25   dimethylxanthine (CT1596S) as an yellow oil.

A solution of 1-(3-(S)-methyl-7-methyloct-6-enyl)-3,7-dimethylxanthine (636 mg, 2
mmol) and m-chloroperoxybenzoic acid (1.04 g; 3 mmol) (50% by wt) in dichloromethane
(15 mL) was stirred for 5 hours. The reaction mixture was diluted with 80 mL of
dichloromethane and washed successively with 20% aqueous sodium sulphite solution(20
30   mL), saturated sodium bicarbonate solution (20 mL), water and brine solutions. The organic
layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure.
The crude product obtained was further purified by flash chromatography over silica gel
using 5% petroleum ether/ethyl acetate eluant to yield 0.56 g (83% yield) 1-(3-(S)-methyl-7-
methyloct-6-enyl)-3,7-dimethylxanthine.

35   Example 23

This example illustrates a synthesis of 1-(4,5-Oxipentyl)-3,7- dimethylxanthine.
Sodium hydride (95%) (1.38 g, 55 mmol) was added to a solution of theobromine (9.0 g, 50
mmol) in dimethylsulfoxide (300 mL). After 20 minutes of stirring, 1-bromo-4-pentene(
7.45 g, 50 mmol) was added. After 16 hours of stirring at room temperature, the reaction

27

was poured into a separatory funnel containing 1 L of water and extracted with
dichloromethane (5 X 200 mL). The organic extracts were combined, washed with water
(100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate and concentrated
under reduced pressure. The crude product obtained was further purified by flash

5   chromatography over silica gel using 20% petroleum ether/ethyl acetate eluant to yield 9.67 g
(92% yield) 1-(4-pentenyl)-3,7-dimethylxanthine (CT1575).

A solution of 1-(4-pentenyl)-3,7-dimethylxanthine (2.48 g, 10 mmol), 4-
methylmorpholine-N-oxide (1.49 g, 12.7 mmol) and potassium osmate dihydrate (7.3 mg;
0.02 mmol) in acetone (20 mL) and water (5 mL) was stirred for 6 hours. A solution of 20%

10   aqueous sodium sulphite (10 ml) was added and stirred for 30 minutes. The reaction mixture
was extracted with 25% ethanol/dichloromethane (4 X 250 mL). The combined organic
extracts were dried over anhydrous magnesium sulfate and concentrated under reduced
pressure. The crude product obtained was further purified by flash chromatography over
silica gel using ethyl acetate eluant to yield 2.5 g (88% yield) of 1-(4,5-dihydroxypentyl)-

15   3,7-dimethylxanthine (CT1584).

1-(4,5-Dihydroxypentyl)-3,7-dimethylxanthine (2.13 g, 7.6 mmol) was stirred with
hydrogen bromide (4.74 mL, 6.15 g of a 30% solution in acetic acid, 22.8 mmol) for 90
minutes. The mixture was then added to a flask containing 50 mL aqueous sodium
bicarbonate solution and 50 mL dichloromethane. After 10 minutes of vigorous stirring, the

20   layers were separated and the aqueous portion washed with dichloromethane (3 X 50 mL).
The organic portions were combined, dried over magnesium sulfate, and the solvent
evaporated to yield 3.4 g (96%) 1-(4-acetoxy-5-bromopentyl)-3,7-dimethylxanthine as a
yellow oil. Without further purification, the oil was taken up in methanol (25 mL) and
treated with a solution of sodium methoxide (prepared from 0.2 g, 8.7 mmol sodium, and 25

25   mL methanol). After 30 minutes most of the solvent was removed under reduced pressure
and the residue extracted with dichloromethane (3 X 50 mL). The organic portions were
combined and dried over magnesium sulfate to obtain an off-white solid purified by column
chromatography over silica gel using ethyl acetate/(15%) acetone eluant to yield 1.0 g (50%
yield) of 1-(4,5-Oxipentyl)-3,7-dimethylxanthine.

30   **Example 24**

This example illustrates a synthesis of 1-(10,11-Oxidoundecanyl)-3,7-
dimethylxanthine (CT1594). Sodium hydride(95%) (1.26 g, 50 mmol) was added to a
solution of theobromine (7.2g, 40 mmol) in dimethylsulfoxide (300 mL). After 20 minutes
of stirring, undecenylmesylate (7.95 g, 30 mmol) was added and stirred for 12 hours at room

35   temperature. The reaction was warmed to 70-80°C and stirred for 4 hours. The reaction
mixture was then poured into a separatory funnel containing 1 L of water and extracted with
dichloromethane (5 X 200 mL). The organic extracts are combined, washed with water (100
mL) and brine (100 mL), dried over anhydrous magnesium sulfate and concentrated under
reduced pressure. The crude product obtained was further purified by flash chromatography

over silica gel (eluant: 20% hexane/dichloromethane) to yield 4.6 g (46.3% yield) 1-(10-Undecenyl)-3,7-dimethylxanthine (CT2501).

A solution of 1-(10-undecenyl)-3,7-dimethylxanthine (4.3 g, 13 mmol), 4-methylmorpholine-N-oxide (1.942 g, 16.6 mmol) and potassium osmate dihydrate (9.5 mg; 0.026 mmol) in acetone (45 mL) and water (10 mL) was stirred for 6 hours. A solution of 20% aqueous sodium sulphite (12 ml) was added and stirred for 30 minutes. The reaction mixture was extracted with 25% ethanol/dichloromethane (4 X 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure and purified by flash chromatography over silica gel using methanol (5%)/dichloromethane eluant to yield 3.6 g (76% yield) 1-(10,11-dihydroxyundecanyl)-3,7-dimethylxanthine (CT1592).

1-(10,11-Dihydroxyundecanyl)-3,7-dimethylxanthine (3.6 g, 10 mmol) was stirred with hydrogen bromide (6.2 mL, 8.4 g of a 30% solution in acetic acid, 31.1 mmol) for 90 minutes. The mixture was then added to a flask containing 100 mL aqueous sodium bicarbonate solution and 75 mL dichloromethane. After 10 minutes of vigorous stirring the layers were separated and the aqueous portion washed with dichloromethane (3 X 75 mL). The organic portions were combined, dried over magnesium sulfate, and evaporated to give 1-(10-acetoxy-11-bromoundecanyl)-3,7-dimethylxanthine (3.6 g). Without further purification, the bromoacetate was taken up in methanol (25 mL) and treated with a solution of sodium methoxide (prepared from 0.28 g, 12.2 mmol sodium, and 25 mL methanol). After 30 minutes, most of the solvent was removed under reduced pressure and the residue extracted with dichloromethane (3 X 75 mL). The organic portions were combined, dried over magnesium sulfate and concentrated under reduced pressure to obtain an off-white solid which was purified by column chromatography over silica gel using dichloromethane/(3%) methanol eluant to yield 2.0 g (57% yield) 1-(10,11-Oxidoundecanyl)-3,7-dimethylxanthine.

Example 25

This example illustrates a synthesis of 1-(5,6-Oxidohexyl)glutarimide (CT-1605M). Sodium hydride (425 mg, 17.7 mmol) was added to a solution of glutarimide (2.00 g, 7.7 mmol) in dimethyl sulfoxide (40 mL). After 20 minutes of stirring, 6-bromo-1-hexene (2.90 g, 17.7 mmol) is added. After 20 hours of stirring, the reaction was poured into a separatory funnel containing 100 mL water and extracted with dichlormethane (4 X 50 mL). The organic portions were combined, washed with water (50 mL) and brine (50 mL) and dried to yield 2.92 g (85% yield) 1-(5-Hexenyl)glutarimide (CT1600) as a colorless oil.

1-(5-Hexenyl)glutarimide (630 mg, 3.2 mmol) was dissolved in dichlormethane (10 mL) and aqueous sodium bicarbonate (2.20 g, 26 mmol in 10 mL water) was added followed by m-chloroperoxybenzoic acid (2.5 g of 50% MCPBA by wt, 7.2 mmol). After 17 hours, sodium metabisulfite (1.7 g, 9.0 mmol) was added. After 30 minutes, the reaction mixture was extracted with dichlormethane (3 x 10 mL). Organic portions were combined and washed with sodium bicarbonate (saturated solution, 10 mL). Purification by

chromatography on silica using 10% ethanol/dichlormethane yielded 180 mg (0.9 mmol, 27% yield) 1-(5,6-Oxidohexyl)glutarimide (CT1605).

Example 26

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This example illustrates a synthesis of N-(8,9-Oxidononyl)glutarimide (CT1606). Sodium hydride (1.02 g, 44 mmol) was added to a solution of glutarimide (5.00 g, 44 mmol) in dimethyl sulfoxide (150 mL). After 20 minutes of stirring, 9-bromo-1-nonene (9.02 g, 44 mmol) was added. After 16 hours of additional stirring at room temperature, the reaction was poured into a separatory funnel containing 100 mL water and extracted with dichlormethane (3 X 70 mL). The organic portions were combined, washed with water (2 X 40 mL) and brine (50 mL) and dried to yield 10.09 g (97%) of 1-(8-Nonenyl)glutarimide (CT1604) as a colorless oil.

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1-(8-Nonenyl)glutarimide (2.00 g, 8 mmol) was dissolved in dichlormethane (15 mL) and aqueous sodium bicarbonate (3.20 g, 38 mmol in 20 mL water) was added followed by *m*-chloroperoxybenzoic acid (4.5 g of 50% MCPBA by wt, 13 mmol). After 17 hours sodium metabisulfite was added slowly until no foaming was observed. After 30 minutes of stirring, the layers were separated and the aqueous layer extracted with dichlormethane (3 x 30 mL). The organic portions were combined and washed with sodium bicarbonate (saturated solution, 30 mL), water (20 mL), and brine (20 mL). The residue was purified using chromotography on silica with ether to yield 756 mg (36% yield) N-(8,9-Oxidononyl)glutarimide as a colorless liquid.

Example 27

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This example illustrates a synthesis of N-(11,10-Oxidoundecyl)glutarimide (CT1611). Sodium hydride (95%) (168 mg, 7 mmol) was added to a solution of glutarimide (565.6 mg, 5 mmol) in dimethyl sulfoxide (15 mL). After 20 minutes of stirring, 1-bromundec-10-ene (1.165 g, 5 mmol) was added and stirred for 12 hours at room temperature. The reaction mixture was then poured into a separatory funnel containing 100 mL of water and extracted with dichlormethane (5 X 75 mL). The organic extracts were combined, washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 20% ethyl acetate/hexane eluant to yield 0.777g (58.6% yield) N-(10-Undecenyl)glutarimide (CT1610).

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A solution of N-(10-Undecenyl)glutarimide (0.6 g, 2.24 mmol) and *m*-chloroperoxybenzoic acid (1.16 g; 3.37 mmol) (50% by wt) in dichloromethane (15 mL) were stirred for 5 hours. The reaction mixture was diluted with 20 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (10 mL), saturated sodium bicarbonate solution (10 mL), water (10 mL) and brine solutions (10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over

silica gel using 80% petroleum ether/acetone eluant to yield 0.6 g (94% yield) of N-(11,10-Oxidoundecyl)glutarimide.

Example 28

This example illustrates a synthesis of N-(10,11-Oxidoundecyl)-2-piperidone

5   (CT1618). A mixture of potassium hydroxide (1.55 g, 25 mmol, pellets ground in mortar and pestle) and tetrabutylammonium bromide (1.61 g, 5.0 mmol) was stirred in dry tetrahydrofuran (10 mL). A solution of d-valerolactam (2.5 g, 25 mmol) and 1-bromo-10-undecene (Lancaster, 5.9 g, 25 mmol) in tetrahydrofuran (15 mL) was added by syringe pump over 1 hour. After stirring for a further 6 hours. Water (60 mL) and dichloromethane

10 (60 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 50 mL). The combined organic layers were washed with water (50 mL) and saturated salt solution (50 mL) and then dried with sodium sulfate. The residue was further purified by chromatography using silica and 30% hexane, ethyl acetate to yield 2.88 g (46% yield) of N-(10-Undecenyl)-2-piperidone (CT1616) as a

15 colorless oil.

To a mixture of N-(10-Undecenyl)-2-piperidone (4.00 g, 16 mmol) and a 60 % aqueous solution of N-methylmorpholine-N-oxide (5 mL, 29 mmol) in water (10 mL) and acetone (20 mL) was added potassium osmate dihydrate (12 mg, .03 mmol). After stirring for 3 days, the mixture was treated with sodium dithionite (100 mg). After 30 minutes,

20 dichloromethane (50 mL) and water (30 mL) were added and the organic layer separated. The aqueous layer was extracted with dichloromethane/10% methanol (2 X 70 mL). The combined organic extracts were dried over sodium sulfate and the solvents evaporated under vacuum. The residue was purified by chromatography using silica and ethyl acetate/methanol in a 0-20% gradient to yield 4.21 g (93%) N-(10,11-Dihydroxyundecyl)-2-

25 piperidone (CT1617) as a colorless oil.

To N-(10,11-dihydroxyundecyl)-2-piperidone (4.21 g, 14.8 mmol) was added 30% hydrogen bromide-acetic acid (8.7 mL) and the mixture was then stirred for 1 hour. The solution was poured carefully into a mixture of sodium bicarbonate (15 g), ice water (150 mL), and dichloromethane (100 mL). After carbon dioxide evolution has subsided, the

30 organic layer was separated and the aqueous layer extracted with dichloromethane (2 X 80 mL). The combined organic layers was dried over sodium sulfate and the solvent evaporated under vacuum to give 1-(10-acetoxy-11-bromoundecyl)-2-piperidone (4.9 g, 89% yield) as a viscous oil which dissolves in methanol (10 mL). A 1 M sodium methoxide (15 mL, 15 mmol) in methanol solution was added all at once. After stirring for 1 hour, the solution was

35 treated with water (50 mL) and then extracted with dichloromethane (3 X 50 mL). The combined extracts were dried over sodium sulfate and the solvent evaporated under vacuum. The residue was purified by chromatography using ethyl acetate to yield 2.40 g (61% yield) N-(10,11-Oxidoundecyl)-2-piperidone as a colorless oil.

Example 29

This example illustrates a synthesis of N-(9,10-Oxidodecyl)piperidine (CT1619). Sodium hydride (95%) (864 mg, 36 mmol) was added to a solution of piperidine (2.554 g, 30 mmol) in dimethyl sulfoxide (75 mL). After 20 minutes of stirring, 1-bromundec-10-ene
5   (6.99 g, 5 mmol) was added and stirred for 12 hours at room temperature. The reaction mixture was then poured into a separatory funnel containing 100 mL of water and extracted with dichlormethane (5 X 75 mL). The organic extracts were combined, washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography
10 over silica gel using 5% methanol/dichloromethane eluant to yield 3.12 g (44% yield) N-(10-undecenyl)piperidine (CT1615).

A solution of N-(10-undecenyl)piperidine (3.1 g, 13 mmol), 4-methylmorpholine-N-oxide (1.84 g, 15.7 mmol) and potassium osmate dihydrate (13 mg) in acetone (64 mL) and water (16 mL) were stirred for 6 hours. The reaction was quenched by the addition of 25 mL
15 of a saturated solution of sodium sulphite and stirred for 15 minutes. The reaction mixture was then extracted with ethyl acetate (4x 100 mL), the combined organic extract was dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 10% methanol/ethyl acetate eluant to yield 2.5 g (83.4% yield) N-(11,10-
20 dihydroxyundecyl)piperidine (CT1622).

A mixture of N-(11,10-dihydroxyundecyl)piperidine (2.0g, 7.4mmol) and a 30% solution of hydrogen bromide in acetic acid (4.45 mL, 22 mmol) was stirred for 90 minutes. The mixture was then added to a flask containing aqueous sodium bicarbonate solution (15 g in 40 mL) and dichloromethane (50 mL). After 10 minutes of vigorous stirring, the layers
25 were separated and the aqueous portion extracted with dichloromethane (2 X 50 mL). The combined organic portions were dried over sodium sulfate. The solvent was evaporated to give 1-(10-acetoxy-11-bromoundecyl)piperidine which was used without further purification. Bromoacetate was dissolved in methanol (10 mL) and treated with a 1 M solution of sodium methoxide (8 mL). After 30 minutes, the reaction mixture was added to water (30 mL) and
30 extracted with dichloromethane (3 X 50 mL). The organic extracts were combined, washed with water (25 mL) and brine solution (25 mL) and then dried over anhydrous magnesium sulphate solution and concentrated under reduced pressure. The crude product obtained was further purified by column chromatography over alumina (grade-II) using 10% methanol/ethyl acetate eluant to yield 1.5 g (80.6%) N-(9,10-Oxidodecyl)piperidine.
35 Example 30

This example illustrates a synthesis of 1-Methyl-3-(8,9-oxidononyl)uracil (CT1804). Sodium hydride (365 mg, 16 mmol) was added to a stirring solution of 1-methyluracil (2.00 g, 16 mmol) in dimethyl sulfoxide (40 mL). After 15 minutes, 6-bromo-1-nonene (3.26 g, 16 mmol) was added and the mixture stirred for 3 days. The reaction was then poured into

water (50 mL) and extracted with dichloromethane (3 X 60 mL). The combined organic layers were washed with water (50 mL), and aqueous saturated salt solution (30 mL) was then dried over sodium sulfate. The solvent was evaporated under vacuum to yield 3.72 g (94%) 1-methyl-3-(8-nonenyl)uracil (CT-1817) as a colorless oil which solidified upon

5   standing.

A solution of 1-methyl-3-(8,9-nonenyl)uracil (3.72 g, 15 mmol), 4-methylmorpholine-N oxide (2.10 g, 18 mmol), and potassium osmate (IV) dihydrate (11 mg, 3.0×10^{-5} mmol) in acetone (20 mL) and water (10 mL) are stirred for 2 days. After addition of sodium hydrosulfite (100 mg) to quench the catalyst, the reaction mixture was

10   extracted with dichloromethane (4 X 50 mL). The combined organic layers were dried over sodium sulfate and the solvent evaporated under vacuum to give an oily residue. Crystallization of the residue from ether/dichloromethane yields 2.66 g (63% yields) 3-(8,9-dihydroxynonyl)-1-methyluracil (CT1818) as white crystals.

A mixture of 3-(8,9-dihydroxynonyl)-1-methyluracil (2.15 g, 7.6 mmol) and a 30%

15   solution of hydrogen bromide in acetic acid (4.5 mL, 23 mmol) were stirred for 6 hours. The reaction mixture was added slowly to a mixture of sodium bicarbonate (8.4 g, 0.1 mol), water (30 mL), and dichloromethane (30 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 X 40 mL). The combined organic layers were washed with aqueous saturated salt solution (20 mL) and dried over sodium sulfate. The solvent was

20   removed under vacuum to yield 2.89 g (97% yield) 3-(8-acetoxy-9-bromononyl)-1-methyluracil (CT1801) as a thick, slightly orange oil.

To a solution of 3-(8-acetoxy-9-bromononyl)-1-methyluracil (2.89 g, 7.4 mmol) in methanol (10 mL) was added a 1 M methanol solution of sodium methoxide (8 mL). After 3 hours, the reaction mixture was poured into water (30 mL) and extracted with

25   dichloromethane (3 X 60 mL). The combined organic layers were washed with water (30 mL) and aqueous saturated salt solution (30 mL), then dried over sodium sulfate. The solvent was evaporated under vacuum and the residue crystallized in ether to yield 1.61 (82% yield) 1-methyl-3-(8,9-oxidononyl)uracil.

Example 31

30   This example illustrates a synthesis of 3-(5,6-Oxidohexyl)-1-methyluracil (CT1808). Sodium hydride (86 mg, 3.6 mmol) was added to a stirring solution of 1-methyluracil (500 mg, 4 mmol) in dimethyl sulfoxide (25 mL). After 15 minutes, 6-bromo-1-hexene (647 mg, 4 mmol) was added and the mixture stirred further for 20 hours. The reaction mixture was then poured into water (50 mL) and extracted with 20% ethanol/dichloromethane (3 X 50

35   mL). The combined organic layers were washed with aqueous saturated salt solution (20 mL) and dried over sodium sulfate. The solvent was evaporated under vacuum to give a residue which was purified by chromatography with silica and ethyl acetate to yield 598 g (72% yield) of 3-hexenyl-1-methyluracil (CT1800).

A solution of 3-(5-hexenyl)-1-methyluracil (598 mg, 2.9 mmol), 4-   ·uei
methylmorpholine-N oxide (408 mg, 3.5 mmol), and a 2.5% solution in *t*-butanol of osmium
tetroxide (3 drops) in acetone (15 mL) and water (5 mL) was stirred for 3 days. After
addition of a saturated solution of sodium hydrosulfite (10 mL) and 15 minutes, the reaction

5   mixture was added to water (15 mL) and extracted with 20% ethanol/dichloromethane (4 X
40 mL). The combined organic layers were dried over sodium sulfate and the solvent is
evaporated under vacuum to give 461 mg (66%) 3-(5,6-dihydroxyhexyl)-1-methyluracil
(CT1811) as a colorless oil.

A mixture of 3-(5,6-dihydroxyhexyl)-1-methyluracil (350 mg, 1.4 mmol) and a 30 %

10   solution of hydrogen bromide in acetic acid (0.87 mL, 4.3 mmol) was stirred for 45 minutes.
The mixture was then added to a mixture of sodium bicarbonate (1.6 g), water (10 mL) and
dichloromethane (20 mL). After 15 minutes of vigorous stirring, the layers were separated
and the aqueous layer extracted with dichloromethane (3 X 40 mL). The combined organic
layers were dried over sodium sulfate, then evaporated under vacuum to give 3-(5-acetoxy-6-

15   bromohexyl)-1-methyluracil (500 mg, 100% yield).   .·

Bromoacetate was used in the next step without further purification. A solution of 3-
(5-acetoxy-6-bromohexyl)-1-methyluracil (360 mg, 1.0 mmol) in methanol (5 mL) was
treated with a 1 M methanol solution of sodium methoxide (1.3 mL). After 15 minutes, the
reaction solution was poured into water (10 mL) and extracted with dichloromethane (3 X 30

20   mL). The combined organic layers were dried over sodium sulfate and the solvent was
evaporated under vacuum to yield 150 mg (67% yield) 3-(5,6-oxidohexyl)-1-methyluracil as
a colorless oil.

Example 32

This example illustrates a synthesis of 3-(5,6-oxidohexyl)-2-methyldihydrouracil

25   (CT1820). Sodium hydride (288 mg, 12 mmol) was added to a solution of N-
methylhydrouracil (1.54 g, 12 mmol) and 1-bromo-5-hexene (1.63g, 10 mmol) in 20 mL of
dimethyl sulfoxide at room temperature and stirred for 12 hours. The reaction mixture was
then quenched with water (80 mL) and extracted with dichloromethane (3x100 mL). The
combined organic extract was washed with saturated aqueous salt solution solution (50 mL),

30   dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The
crude product obtained was further purified by flash chromatography over silica gel using
20% acetone/hexane eluant to yield 2.0 g (79%) 3-(5-hexenyl)-1-methylhydrouracil
(CT1812).

A solution of 3-(5-hexenyl)-1-methylhydrouracil (1.5 g, 7.1 mmol), and *m*-

35   chloroperoxybenzoic acid (3.68 g, 10.7 mmol) (50% by wt) in dichloromethane (60 mL) was
stirred for 5 hours. The reaction mixture was quenched with 20% aqueous sodium sulphite
solution(75 mL) and extracted with dichloromethane (3x100 mL). The combined organic
extract is washed successively with saturated aqueous saturated salt solution (50 mL),
saturated sodium bicarbonate solution (50 mL), water (50 mL), aqueous saturated salt

solution (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 30% acetone/ hexane eluant to yield 1.27 g (78.8 % yield) 3-(5,6-oxidohexyl)-2-methyldihydrouracil (CT1820).

5   **Example 33**

This example illustrates a synthesis of 3-(10,11-Oxidoundecanyl)-1-methylhydrouracil (CT-1822). Sodium hydride (288 mg, 12 mmol) was added to a solution of N-methylhydrouracil (1.54 g, 12 mmol) and 1-bromo-10-undecene (2.33 g, 10 mmol) in 20 mL of dimethyl sulfoxide at room temperature and stirred for 12 hours. The reaction

10   mixture was then quenched with water (80 mL) and extracted with dichloromethane (3x100 mL). The combined organic extract was washed with saturated aqueous salt solution (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using a 20% acetone/hexane eluent to yield 2.04 g (61.8% yield) of 3-(10-undecenyl)-1-

15   methylhydrouracil (CT1819).

A solution of 3-(10-undecenyl)-1-methylhydrouracil (0.28 g, 1 mmol), and *m*-chloroperoxybenzoic acid (0.517 g, 1.5 mmol) (50% by wt) in dichloromethane (6 mL) was stirred for 5 hours. The reaction mixture was diluted with 75 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution(25 mL), saturated NaHCO3

20   solution (25 mL), water (25 mL), aqueous saturated salt solution (25 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using 20% acetone/ hexane eluant to yield 0.22 g (74.3 %) 3-(10,11-Oxidoundecanyl)-1-methylhydrouracil.

Example 34

25   This example illustrates a synthesis of 3-(5,6-Oxidohexyl)-1-methylthymine (CT1906). Sodium hydride (343 mg, 14 mmol) was added to a stirring solution of 1-methylthymine (Sigma, 2.00 g, 14 mmol) in dimethylsulfoxide (30 mL). After 15 minutes, 6-bromo-1-hexene (Lancaster, 2.30 g, 14 mmol) was added and stirring continued for 69 hours. The reaction mixture was then poured into water (100 mL) and extracted with

30   dichloromethane (4 X 50 mL). The combined organic layers were washed with saturated aqueous salt solution (40 mL) and dried over sodium sulfate. The solvent was evaporated under vacuum to give a residue which was crystallized in dichloromethane/ ethyl ether to yield 2.80 g (88% yield) 3-(5-hexenyl)-1-methylthymine (CT1905).

A solution of 3-(5-hexenyl)-1-methylthymine (2.00 g, 9 mmol), 4-methylmorpholine-

35   N oxide (1.17 mg, 10 mmol), and a 2.5% sol. in *t*-butanol of osmium tetroxide (0.15 mL) in acetone (15 mL) and water (10 mL) was stirred for 20 hours. After addition of a saturated solution of sodium hydrosulfite (10 mL) and 15 minutes of stirring, the reaction mixture was extracted with 20% ethanol/dichloromethane (4 X 40 mL). The combined organic layers were dried over sodium sulfate and the solvent evaporated under vacuum to a give white

solid residue. The solid was recrystallized in ethanol to yield 2.00 g (89%) of 3-(5,6-
dihydroxyhexyl)-1-methylthymine (CT1907).

A mixture of 3-(5,6-dihydroxyhexyl)-1-methylthymine (1.65 g, 6.4 mmol) and a 30%
solution of hydrogen bromide in acetic acid (3.8 mL, 19.3 mmol) in water (5 mL) and
5   acetone (10 mL) was stirred for 1.5 hours. The mixture was then added to a flask containing
sodium bicarbonate (6.7 g), water (40 mL) and dichloromethane (50 mL). After 15 minutes
of vigorous stirring, the layers were separated and the aqueous layer washed with
dichloromethane (2 X 50 mL). The combined organic layers were dried over sodium sulfate.
The solvent was evaporated under vacuum to yield 2.30 g (100%) of 3-(5-acetoxy-6-
10 bromohexyl)-1-methylthymine as a yellow oil. The bromoacetate was used in the next step
without further purification. A solution of 3-(5-acetoxy-6-bromohexyl)-1-methylthymine
(2.30 g, 6.4 mmol) in methanol (10 mL) was treated with a 1 M methanol solution of sodium
methoxide (7 mL). After stirring for 15 minutes, the solution was poured into water (60 mL)
and extracted with 20% ethanol/dichloromethane (2 X 70 mL). The combined organic layers
15 were dried over sodium sulfate and the solvent evaporated under vacuum to yield 1.30 g
(85%) 3-(5,6-oxidohexyl)-1-methylthymine as a white solid.

Example 35

This example illustrates a synthesis of 1-Methyl-3-(8,9-oxidononyl)thymine
(CT1910). Sodium hydride (343 mg, 14 mmol) was added to a stirring solution of 1-
20 methylthymine (2.00 g, 14 mmol) in dimethylsulfoxide (40 mL). After 15 minutes, 9-
bromo-1-nonene (2.93 g, 14 mmol) was added and the mixture stirred for 20 hours. The
reaction was poured into 40 mL water and extracted with dichloromethane (3 X 50 mL). The
organic layers were combined, washed with water (40 mL), saturated aqueous salt solution
(20 mL), and dried over sodium sulfate. The solvent was evaporated to yield 2.76 g (73%
25 yield) 1-Methyl-3-(8-nonenyl)thymine (CT1917) as a colorless oil which solidified upon
standing.

A solution of 1-methyl-3-(8-nonenyl)thymine (2.63 g, 9.9 mmol), 4-
methylmorpholine-N oxide (1.39 g, 12 mmol), and potassium osmate (IV) dihydrate (7 mg, 2
x 10^{-5} mol) in acetone (20 mL) and water (10 mL) was stirred for 18 hours. After addition
30 of a saturated aqueous solution of sodium hydrosulfite (10 mL) and 15 minutes of stirring,
the reaction mixture was extracted with dichloromethane (50 mL) and with
dichloromethane/20% methanol (2 X 50 mL). The combined organic layers were washed
with water (15 mL) and saturated aqueous salt solution (15 mL), and then dried over sodium
sulfate. The solvent was evaporated under vacuum to give a white solid residue. The solid
35 was recrystallized in ethanol to yield 2.68 g (91% yield) 3-(8,9-dihydroxynonyl)-1-
methylthymine (CT1918).

A mixture of 3-(8,9-dihydroxynonyl)-1-methylthymine (2.16 g, 7.6 mmol) and a 30%
solution of hydrogen bromide in acetic acid (4.5 mL, 23 mmol) was stirred for 1 hour. The
reaction was added slowly to a beaker containing sodium bicarbonate (8.4 g, 0.1 mol), ice

water (30 mL), and dichloromethane (30 mL). The layers were separated and the aqueous layer extracted with dichloromethane (2 X 60 mL). The combined organic layers were washed with water (30 mL), saturated aqueous salt solution (30 mL), and dried over sodium sulfate. The solvent was removed to yield 2.59 g (85% yield) 3-(8-acetoxy-9-bromononyl)-1-methylthymine (CT1908) as a thick, slightly orange oil.

To a solution of 3-(8-acetoxy-9-bromononyl)-1-methylthymine (2.04 g, 5.1 mmol) in methanol (15 mL) was added a 1 M solution of sodium methoxide (6 mL). After 3 hours, the reaction was poured into water (20 mL) and extracted with dichloromethane (3 X 30 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous salt solution (20 mL), then dried over sodium sulfate. The solvent was evaporated under vacuum and the residue crystallized in dichloromethane-ether to yield 1.09g (76% yield) white crystals of 1-methyl-3-(8,9-oxidononyl)thymine.

Example 36

This example illustrates a synthesis of 3-(11,10-Oxidoundecyl)-1-methylthymine (CT1932). Sodium hydride (95%) (168 mg, 7 mmol) was added to a solution of 1-methylthymine (700.5 mg, 5 mmol) in dimethylsulfoxide (15 mL). After 20 minutes of stirring, 1-bromundec-10-ene (1.165 g, 5 mmol) was added and stirred for 12 hours at room temperature. The reaction mixture was then poured into a separatory funnel containing 100 mL of water and extracted with dichloromethane (5 X 75 mL). The organic extracts were combined, washed with water (50 mL) and saturated aqueous salt solution (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using a 20% ethyl acetate/hexane eluant to yield 1.22 g (83.7% yield) 3-(10-undecenyl)-1-methylthymine (CT1931).

A solution of 3-(10-undecenyl)-1-methylthymine (2 g, 6.8 mmol), and *m*-chloroperoxybenzoic acid (3.5 g, 10.2 mmol) (50% by wt) in dichloromethane (50 mL) was stirred for 5 hours. The reaction mixture was diluted with 80 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (30 mL), saturated sodium bicarbonate solution (30 mL), water (30 mL) and brine solutions (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using a 70% hexane/ethyl acetate eluant to yield 1.73 g (82% yield) 3-(11,10-Oxidoundecyl)-1-methylthymine (CT1932).

Example 37

This example illustrates a synthesis of 1-(3,4-Oxidobutyl)-3,7-dimethylxanthine (CT2513). Sodium hydride (95%) (1.26 g, 50 mmol) was added to a solution of theobromine (7.2g, 40 mmol) in dimethylsulfoxide (300 mL). After 20 minutes of stirring, 4-bromobutene (5.4 g, 40 mmol) was added. After 16 hours of stirring at room temperature, the reaction was poured into a separatory funnel containing 1 L of water and extracted with

dichloromethane (5 X 200 mL). The organic extracts were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using a 20% petroleum ether/ethyl acetate eluant to yield 6.3

5   g (67.7% yield) 1-(3-Butenyl)-3,7-dimethylxanthine (CT2503) as a white solid.

A solution of 1-(3-Butenyl)-3,7-dimethylxanthine (5.8 g, 24.8 mmol), 4-methylmorpholine-N-oxide (3.63 g, 31 mmol) and potassium osmate dihydrate (18.3 mg; 0.05 mmol) in acetone (40 mL) and water (10 mL) was stirred for 6 hours. A solution of 20% aqueous sodium sulphite (20 ml) was added and stirred for 30 minutes. The reaction

10   mixture was extracted with 25% ethanol/dichloromethane (4 X 250 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using an acetone eluant to yield 4.5 g (67.7% yield) 1-(3,4,-dihydroxybutyl)-3,7-dimethylxanthine (CT2509).

15   1-(3,4-Dihydroxybutyl)-3,7-dimethylxanthine (3.98 g, 14.9 mmol) was stirred with hydrogen bromide (9.2 mL, 12.06 g of a 30% solution in acetic acid, 44.7 mmol) for 90 minutes. The mixture was then added to a flask containing 200 mL aqueous saturated sodium bicarbonate solution and 75 mL dichloromethane. After 10 minutes of vigorous stirring, the layers were separated and the aqueous portion washed with dichloromethane (3

20   X 150 mL). The organic portions were combined, dried (magnesium sulfate), and evaporated to give 1-(3-acetoxy-4-bromobutyl)-3,7-dimethylxanthine(5.6 g). Without further purification, the bromoacetate was taken up in methanol (50 mL) and treated with a solution of sodium methoxide (prepared from 0.414 g, 12.2 mmol sodium, and 25 mL methanol). After 30 minutes, most of the solvent was removed under reduced pressure and

25   the residue extracted with 25% ethanol/dichloromethane (3 X 150 mL). The organic portions were combined, dried (magnesium sulfate) and concentrated under reduced pressure to give an off-white solid which is purified by column chromatography over silica gel using an ethyl acetate eluant to yield 2.2 g (58 % yield) 1-(3,4-Oxidobutyl)-3,7-dimethylxanthine.

Example 38

30   This example illustrates a synthesis of 1-(11,12-Oxidododecyl)-3,7-dimethylxanthine (CT2518). To a suspension of magnesium (6.4 g, 265 mmol) and a crystal of iodine in tetrahydrofuran (40 mL) was added 10-undecenyl bromide (12.25 g, 53.0 mmol, available from MTM) in tetrahydrofuran (30 mL) over 30 minutes and the reaction stirred for a further 30 minutes after the addition was complete. The solution was added via a canula over 5

35   minutes to a suspension of paraformaldehyde (1.80 g, 60.0 mmol) in tetrahydrofuran (40 mL) and stirred at 25°C for 16 hours. Saturated ammonium chloride (80 mL) is added and extracted with diethyl ether (2 x 100 mL). The combined organic extracts are dried using magnesium sulfate and evaporated to give a residue which is distilled at 2 mm Hg to yield 6.53 g (67% yield, b.p. 105-107°C) of 11-dodecenyl alcohol as a clear liquid.

To a solution of 11-dodecen-1-ol (5.5 g, 29.9 mmol) in dichloromethane (70 mL) at 0 °C was added methanesulfonyl chloride (3.55 g, 2.40 mL, 31.0 mmol) followed by triethylamine (4.38 g, 46.0 mmol). After stirring for 10 minutes at 0°C, the reaction was allowed to warm to 25°C and stirred for 2 hours. The reaction was poured into water (60

5   mL), separated and washed with dichloromethane (50 mL). The organic portions were combined, dried using magnesium sulfate, and evaporated to yield 12-methanesulfonyl-1-dodecene as a yellow oil which was then used without further purification.

To a suspension of sodium theobromine (6.00 g, 30.0 mmol) in dimethylsulfoxide (60 mL) was added 12-methanesulfonyl-1-dodecene and the reaction stirred for 16 hours at 60°C.

10   The mixture was then poured into water (120 mL) and extracted with diethyl ether (2 x 100 mL). The organic portions were combined, dried using magnesium sulfate and evaporated to give a cream solid. Recrystallization from ethyl acetate/hexane 1:1 yields 6.97 g (67% yield) 1-(11-dodecenyl)-3,7-dimethylxanthine (CT2516) as a white solid.

A solution of 1-(11-Dodecenyl)-3,7-dimethylxanthine (4.70 g, 13.6 mmol), 4-

15   methylmorpholine-N-oxide (4.79 g, 40.7 mmol) and potassium osmate dihydrate (52 mg, 0.14 mmol) in acetone/water 1:2 (75 mL) was stirred for 16 hours. Water (50 mL) and sodium sulfite (5 g) were added and the mixture stirred for 1 hour. The reaction mixture was extracted with dichloromethane (3 x 100 mL), dried using magnesium sulfate and evaporated to obtain a pale green solid. Recrystallization from hot ethyl acetate yields 4.32 g (84%

20   yield) 1-(11,12-dihydroxydodecyl)-3,7-dimethylxanthine (CT2517) as a white solid.

1-(11,12-Dihydroxydodecyl)-3,7-dimethylxanthine (2.50 g, 6.58 mmol) was stirred with hydrogen bromide (6.39 mL of a 30% solution in acetic acid, 19.73 mmol) for 2 hours. The mixture was then added over 10 minutes to water (25 mL), ice (30 g) and sodium hydride CO_3 (15 g) and stirred for 30 minutes. The reaction mixture was extracted with

25   dichloromethane (3 x 50 mL), and the combined organic phases were dried using magnesium sulfate and evaporated to obtain 3.18 g (99% yield) of 1-(11-acetoxy-12-bromododecyl)-3,7-dimethylxanthine. Without further purification, this crude product was taken up in methanol (10 mL) and treated with a solution of sodium methoxide (prepared from sodium, 0.160 g, 6.90 mmol, and 20 mL methanol). After 60 minutes, the reaction was added to water (30

30   mL) and extracted with dichloromethane (3 x 50 mL). The organic portions were combined, dried and evaporated to yield 2.20 g (93% yield) 1-(11,12-oxidododecyl)-3,7-dimethylxanthine as a white solid.

<u>Example 39</u>

This example illustrates a synthesis of 1-(9,10-Oxidoctadecyl)-3,7-dimethylxanthine

35   (CT2541). Triphenylphosphine (5.24 g; 20 mmol) was added in portions to a solution of oleyl alcohol (5.37 g; 20 mmol) and carbontetrabromide (6.63 g; 20 mmol) in 400 mL of dichloromethane and stirred for an hour at room temperature. The solvent was removed under reduced pressure and the residue extracted with hexane (3 X 200 mL). Further

purification was done by flash chromatography over silica gel using hexane as eluant to yield 5.82 g (88% yield) of 1-bromo-9-octadecene.

Sodium hydride (95%) (84 mg, 3.5 mmol) was added to a solution of theobromine (0.595 g, 3.2 mmol) in dimethylsulfoxide (15 mL). After 20 minutes of stirring, 1-bromo-9-

5   ctadecene(0.995 g, 3 mmol) was added. After 6 hours of stirring at room temperature, the reaction mixture was warmed to 60°C for 3 hours and then poured into a separatory funnel containing 50 mL of water and extracted with dichloromethane (5 X 40 mL). The organic extracts were combined, washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product

10 obtained was further purified by flash chromatography over silica gel using a 30% acetone/petroleum ether eluant to yield 0.44 g (34 % yield) of)1-(9-octadecenyl)-3,7-dimethylxanthine (CT2539).

A solution of 1-(9-octadecenyl)-3,7-dimethylxanthine (0.15 g, 0.35 mmol) and *m*-chloroperoxybenzoic acid (0.15 g, 0.43 mmol) (50% by wt) in dichloromethane (7 mL) was

15 stirred for 5 hours. The reaction mixture was diluted with 40 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (10 mL), saturated sodium bicarbonate solution (10 mL), water and brine solutions. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using a 30%

20 acetone/hexane eluant to yield 0.73 g (48.4% yield) of 1-(9,10-oxidoctadecyl)-3,7-dimethylxanthine.

Example 40

This example illustrates a synthesis of 1-(4-(S)-Methyl-7,8-oxido-8-methylnonyl)-3,7-dimethylxanthine (CT2548S). To a suspension of magnesium (2.74 g, 140 mmol) and a

25 crystal of iodine in tetrahydrofuran (15 mL) was added (S)-citronellyl bromide (5.0 g, 22.8 mmol) in tetrahydrofuran (10 mL) over 30 minutes and the reaction stirred for a further 30 minutes after the addition was complete. The solution was added via a canula over 5 minutes to a suspension of paraformaldehyde (1.80 g, 60.0 mmol) in tetrahydrofuran (15 mL) and stirred at 25°C for 6 hours. Saturated ammonium chloride (40 mL) was added and extracted

30 with diethyl ether (2 x 30 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated to yield 3.25 g (84% yield) 4-(S)-methyl-8-methylnon-7-enyl alcohol as a clear liquid.

To a solution of 4-(S)-methyl-8-methylnon-7-enyl alcohol (3.25 g, 19.1 mmol) in dichloromethane (50 mL) at 0°C is added methanesulfonyl chloride (2.29 g, 20.0 mmol)

35 followed by triethylamine (3.04 g, 30.0 mmol). After stirring for 10 minutes at 0°C, the reaction was allowed to warm to 25°C and stirred for 3 hours. The reaction was poured into water (50 mL), separated and washed with dichloromethane (50 mL). The organic portions were combined, dried using magnesium sulfate, and evaporated to give the 1-

methanesulfonyl-4-(S)-methyl-8-methylnon-7-ene as a yellow oil which is used without further purification.

To a suspension of sodium theobromine (4.05 g, 20.0 mmol) in dimethylsulfoxide (50 mL) was added 1-methanesulfonyl-4-(S)-methyl-8-methylnon-7-ene and the reaction stirred
5   for 16 hours at 60°C. The mixture was then poured into water (100 mL) and extracted with ethyl acetate (100 mL, 2 x 50 mL). The organic portions were combined, dried using magnesium sulfate, and evaporated to give a residue which was purified by column chromatography (ethyl acetate/hexane) to yield 1.83 g (30% yield) 1-(4-(S)-Methyl-8-methylnon-7-enyl)-3,7-dimethylxanthine (CT2536S) as a white solid.

10   A solution of (0.65 g, 1.96 mmol), 4-methylmorpholine-N-oxide (0.69 g, 5.87 mmol) and potassium osmate dihydrate (7 mg, 0.021 mmol) in acetone/water 1:2 (12 mL) was stirred for 16 hours. Water (10 mL) and sodium sulfite (1 g) were added and the reaction mixture stirred for 1 hour. The reaction mixture was extracted with dichloromethane (3 x 30 ml), dried using magnesium sulfate and the solvent evaporated to yield 0.675 g (94%) of 1-
15   (4-(S)-methyl-7,8-dihydroxy-8-methylnonyl)-3,7-dimethylxanthine (CT2537S) as a colorless oil.

1-(4-(S)-Methyl-7,8-dihydroxy-8-methylnonyl)-3,7-dimethylxanthine (0.37 g, 1.00 mmol) was stirred with hydrogen bromide (1.25 mL of a 30% solution in acetic acid, 3.00 mmol) for 4 hours. The mixture was then added over 10 minutes to water (10 mL), ice (5 g)
20   and sodium bicarbonate (2 g) and stirred for 30 minutes. The reaction mixture was extracted with dichloromethane (2 x 15 mL), and the combined organic phases were dried using magnesium sulfate and the solvent evaporated to yield a residue of 1-(4-(S)-methyl-7-acetoxy-8-bromo-8-methylnonyl)-3,7-dimethylxanthine.

Without further purification, the crude residue was taken up in methanol (5 mL) and
25   treated with a solution of sodium methoxide (prepared from sodium (0.025 g, 1.09 mmol) and 5 mL methanol). After 40 minutes, the reaction mixture was added to water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic portions were combined, dried and the solvent evaporated to yield 0.32 g (92%) 1-(4-(S)-Methyl-7,8-oxido-8-methylnon)-3,7-dimethylxanthine as a white solid.

30   **Example 41**

This example illustrates a synthesis of 1-(4-(R)-Methyl-7,8-oxido-8-methylnon)-3,7-dimethylxanthine (CT2548R). To a suspension of magnesium (2.74 g, 140 mmol) and a crystal of iodine in tetrahydrofuran (15 mL) was added (R)-citronellyl bromide (5.0 g, 22.8 mmol) in tetrahydrofuran (10 mL) over 30 minutes and the reaction stirred for a further 30
35   minutes after the addition was complete. The solution was added via a canula over 5 minutes to a suspension of paraformaldehyde (1.80 g, 60.0 mmol) in tetrahydrofuran (15 mL) and stirred at 25°C for 6 hours. Saturated ammonium chloride (40 mL) was added and extracted with diethyl ether (2 x 30 mL). The combined organic extracts were dried (magnesium

sulfate) and the solvent evaporated to yield 3.25 g (84% yield) 4-(R)-methyl-8-methylnonyl-
7-enyl alcohol as a clear liquid.

To a solution of 4-(R)-methyl-8-methylnonyl-7-enyl alcohol (3.25 g, 19.1 mmol) in
dichloromethane (50 mL) at 0°C is added methanesulfonyl chloride (2.29 g, 20.0 mmol)

5   followed by triethylamine (3.04 g, 30.0 mmol). After stirring for 10 minutes at 0°C, the
reaction was allowed to warm to 25°C and stirred for 3 hours. The reaction was poured into
water (50 mL), separated and washed with dichloromethane (50 mL). The organic portions
were combined, dried using magnesium sulfate and the solvent evaporated to give the 1-
methanesulfonyl-4-(R)-methyl-8-methylnon-7-ene as a yellow oil which was used without

10   further purification.

To a suspension of sodium theobromine (4.05 g, 20.0 mmol) in dimethylsulfoxide (50
mL) was added 1-methanesulfonyl-4-(R)-methyl-8-methylnon-7-ene and the reaction stirred
for 16 hours at 60°C. The mixture was then poured into water (100 mL) and extracted with
ethyl acetate (100 mL, 2 x 50 mL). The organic portions were combined, dried using

15   magnesium sulfate and the solvent evaporated to give a residue which was purified by
column chromatography using ethyl acetate/hexane to yield 1.70 g (28% yield) 1-(4-(R)-
Methyl-8-methylnon-7-enyl)-3,7-dimethylxanthine (CT2536R) as a white solid.

A solution of 1-(4-(R)-Methyl-8-methylnon-7-enyl)-3,7-dimethylxanthine (0.48 g,
1.44 mmol), 4-methylmorpholine-N-oxide (0.51 g, 4.38 mmol) and potassium osmate

20   dihydrate (5 mg, 0.015 mmol) in acetone/water 1:2 (9 mL) was stirred for 16 hours. Water
(10 mL) and sodium sulfite (1 g) were added and the reaction mixture stirred for 1 hour. The
reaction mixture was extracted with dichloromethane (3 x 30 ml) using dried magnesium
sulfate and the solvent evaporated to yield 0.51 g (97% yield) 1-(4-(R)-Methyl-7,8-
dihydroxy-8-methylnonyl)-3,7-dimethylxanthine (CT2537R) as a colorless oil.

25   1-(4-(R)-Methyl-7,8-dihydroxy-8-methylnonyl)-3,7-dimethylxanthine (0.29 g, 0.80
mmol) was stirred with hydrogen bromide (1.00 mL of a 30% solution in acetic acid, 2.40
mmol) for 4 hours. The mixture was then added over 10 minutes to water (10 mL), ice (5 g)
and sodium bicarbonate (2 g) and stirred for 30 minutes. The reaction mixture was extracted
with dichloromethane (2 x 15 mL), the combined organic phases dried using magnesium

30   sulfate and the solvent evaporated to obtain a residue of 1-(4-(R)-methyl-7-acetoxy-8-bromo-
8-methylnonyl)-3,7-dimethylxanthine.

Without further purification, this crude residue was taken up in methanol (5 mL) and
treated with a solution of sodium methoxide (prepared from sodium (0.020 g, 0.85 mmol)
and 5 mL methanol). After 40 minutes, the reaction was added to water (10 mL) and

35   extracted with dichloromethane (3 x 10 mL). The organic portions were combined, dried and
evaporated to yield 0.24 g (86% yield) of 1-(4-(R)-Methyl-7,8-oxido-8-methylnonyl)-3,7-
dimethylxanthine (CT2548R) as a white solid.

Example 42

This example illustrates a synthesis of 1-(3,7-Dimethyl-2,3,6,7-dioxidoctyl)-3,7-dimethylxanthine (CT2552). Sodium hydride (95%) (0.28 g, 12 mmol) was added to a solution of theobromine (2.16 g, 12 mmol) in dimethylsulfoxide (50 mL). After 20 minutes
5   of stirring, geranyl bromide (2.17 g, 10 mmol) was added. After 6 hours of stirring at room temperature, the reaction mixture was warmed to 60°C for 3 hours and then poured into a separatory funnel containing 150 mL of water and extracted with dichloromethane (5 X 75 mL). The organic extracts were combined, washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The
10   crude product obtained was further purified by flash chromatography over silica gel using 30% acetone/petroleum ether eluant to yield 2.1 g (66.5 % yield) 1-(Geranyl)-3,7-dimethylxanthine (CT2545).

A solution of 1-(geranyl)-3,7-dimethylxanthine (0.316 g, 1 mmol), and m-chloroperoxybenzoic acid (1.035 g; 3 mmol) (50% by wt) in dichloromethane (15 mL) was
15   stirred for 6 hours. The reaction mixture was diluted with 80 mL of dichloromethane and washed successively with 20% aqueous sodium sulphite solution (20 mL), saturated sodium hydride CO₃ solution (20 mL), water and brine solutions. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product obtained was further purified by flash chromatography over silica gel using a 30%
20   acetone/hexane eluant to yield 0.25 g (72% yield) 1-(3,7-dimethyl-2,3,6,7-dioxidoctyl)-3,7-dimethylxanthine.

Example 43

This example illustrates a synthesis of 1-(12,13-Oxidotridecyl)-3,7-dimethylxanthine (CT2562). To a suspension of magnesium (4.12 g, 172 mmol) and a crystal of iodine in
25   tetrahydrofuran (40 mL) was added 10-undecenyl bromide (8.00 g, 34.3 mmol) in tetrahydrofuran (30 mL) over 30 minutes and the reaction stirred for a further 30 minutes after the addition was complete. The solution was added via a canula over 5 minutes to a solution of ethylene oxide (2.65 g, 60.0 mmol) in tetrahydrofuran (30 mL) and stirred at 25° C for 16 hours. Saturated ammonium chloride (100 mL) and 1M hydrogen chloride (200
30   mL) were added and extracted with diethyl ether (2 x 200 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated to give a residue which was distilled at 1.5 mm Hg to afford 12-tridecenyl alcohol as a clear liquid (4.11 g, 61%, b.p. 98-101°C).

To a solution of 12-tridecen-1-ol (2.11 g, 10.7 mmol) and carbon tetrabromide (4.37 g, 13.1 mmol) in dichloromethane (15 mL) at 0°C was added triphenyl phosphine (3.45 g,
35   13.1 mmol) in portions over 5 minutes. After stirring for 1.5 hours at 25°C the solvent was evaporated and the residue extracted with hexane (3 x 30 mL), filtering off any solids. The solvent was evaporated to afford 12-tridecenyl bromide as a clear oil which was used without further purification.

43

To a suspension of sodium theobromine (2.22 g, 11.0 mmol) in dimethylsulfoxide (25 mL) was added 12-tridecenyl bromide and the reaction stirred for 16 hours at 60°C. The mixture was then poured into water (80 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic portions were washed with water (3 x 100 mL), dried using

5   magnesium sulfate, and evaporated to give a gummy residue. Purification by column chromatography using an ethyl acetate/hexane eluant yields 1.89 g (50% yield) 1-(12-Tridecenyl)-3,7-dimethylxanthine (CT2555) as a white solid.

A solution of 1-(12-Tridecenyl)-3,7-dimethylxanthine (1.39 g, 3.86 mmol), 4-methylmorpholine-N-oxide (1.36 g, 11.6 mmol) and potassium osmate dihydrate (14 mg,

10   0.040 mmol) in acetone/water 1:2 (25 mL) was stirred for 16 hours. Water (25 mL) and sodium sulfite (2 g) were added and the reaction mixture stirred for 1 hour. The reaction mixture was extracted with dichloromethane (3 x 50 mL), dried using magnesium sulfate and the solvent evaporated to yield 1.25 g (82%) of 1-(12,13-dihydroxytridecyl)-3,7-dimethylxanthine (CT2556) as a white solid.

15   1-(12,13-Dihydroxy-tridecyl)-3,7-dimethylxanthine (1.15 g, 2.92 mmol) was stirred with hydrogen bromide (2.84 mL of a 30% solution in acetic acid, 8.76 mmol) for 2 hours. The mixture was then added over 10 minutes to water (20 mL), ice (15 g) and sodium bicarbonate (5 g) and stirred for 30 minutes. The reaction mixture was extracted with dichloromethane (2 x 50 mL), and the combined organic phases were dried using magnesium

20   sulfate and the solvent evaporated to obtain a residue of 1-(12-acetoxy-13-bromotridecyl)-3,7-dimethylxanthine. Without further purification, this crude residue was taken up in methanol (5 mL) and treated with a solution of sodium methoxide (prepared from sodium, 0.069 g, 3.00 mmol, and 5 mL methanol). After 40 minutes, the reaction mixture was added to water (15 mL) and extracted with dichloromethane (3 x 30 mL). The organic portions

25   were combined, dried and the solvent evaporated to yield 1.00 g (91% yield) 1-(12,13-Oxidotridecyl)-3,7-dimethylxanthine (CT2562) as a white solid.

Example 44

This example illustrates a synthesis of 1-(7,8-*cis*-Oxidodecyl)-3,7-dimethylxanthine (CT2563). 7-*cis*--Decenal (Johnson Matthey Catalog Co., 10.00g, 6.5 mmol) was added

30   dropwise to a stirring suspension of sodium borohydride (2.45 g, 65 mmol) in ethanol (100 mL) at 0°C. The ice bath was allowed to melt and stirring continued for 3 hours. Ammonium chloride solution (sat., 60 mL) was added with water (50 mL) and the mixture was extracted with dichloromethane (3 x 100 mL). The organic extracts were combined and washed with water (50 mL) and brine (50 mL) and dried (sodium sulfate). Evaporation of

35   solvent gave the alcohol 7-*cis*--decen-1-ol as a colorless oil (9.19g, 91% yield).

7-*cis*-Decen-1-ol (5.00 g, 32.1 mmol) and methanesulfonyl chloride (2.5 mL, 3.70 g, 32.3 mmol) in dichloromethane (150 mL) at 0°C is treated dropwise with triethylamine (6.7 mL, 4.9 g, 48 mmol), after which time, the ice bath is allowed to melt. After stirring 3 hours at room temperature, the reaction was poured into a separatory funnel containing saturated

sodium bicarbonate solution (50 mL) and dichloromethane (50 mL). The layers were separated and the aqueous layer washed with dichloromethane (2 X 50 mL). The organic layers were combined, washed with hydrogen chloride solution (50 mL, 1%), water (50 mL), and brine (40 mL), then dried (sodium sulfate). The solvent was removed to yield 6.97 g

5   (92%) 7-*cis*-decene-1-methanesulfonate as a yellow oil. The mesylate was used in the next step without further purification.

1-Sodiotheobromine (6.00 g, 29.7 mmol) and 7-*cis*-decene-1-methanesulfonate (6.97 g, 29.7 mmol) were stirred in dimethylsulfoxide (60 mL) for 15 hours, then at 80°C for 3 hours, then cooled. The reaction mixture was poured into water (100 mL) and extracted with

10   dichloromethane (3 X 60 mL). The organic layers were combined and washed with water (60 mL) and brine (50 mL) and dried using sodium sulfate. Addition of ether and petroleum ether to the residue precipitates a white solid, yielding 3.25 g (32% yield) 1-(7-*cis*-Decenyl)-3,7-dimethylxanthine (CT2560).

1-(7-*cis*-Decenyl)-3,7-dimethylxanthine (0.50 g, 1.6 mmol) in dichloromethane (25

15   mL) was added to a solution of sodium bicarbonate (1.30 g, 16 mmol) in water (20 mL). 4-Chloro-peroxybenzoic acid (326 mg, or 652 mg of a 50% mixture, 1.9 mmol) was added and the reaction mixture stirred at room temperature for 20 hours. Sodium sulfite (100 mg) was added to quench residual MCPBA. To the reaction mixture was added dichloromethane (30 mL) and water (20 mL). The organic layer was separated and the aqueous layer washed with

20   dichloromethane (3 x 30 mL). The organic layers were combined and washed with saturated sodium bicarbonate solution (20 mL), and brine (20 mL) and then dried using sodium sulfate. Removal of solvent results in an oil which solidifies upon standing. The white solid was washed with ether and dried to yield 460 mg (86% yield) of 1-(7,8-*cis*-Oxidodecyl)-3,7-dimethylxanthine.

25   Example 45

This example illustrates a synthesis of 1-(13,14-Oxidotetradecyl)-3,7-dimethylxanthine (CT3503). To a suspension of magnesium (1.86 g, 77.2 mmol) and a crystal of iodine in THF (20 mL) was added 10-undecenyl bromide (6.00 g, 25.8 mmol) in THF (14 mL) over 40 minutes and the reaction stirred for a further 30 minutes after the

30   addition was complete. The solution was added via a canula over 50 minutes to a suspension of copper iodide (0.50 g, 2.58 mmol) and 1-bromo-3-chloropropane (3.84 mL, 38.7 mmol) in THF (20 mL) and stirred at 25°C for 16 hours. Sulfuric acid (1.0 M, 50 mL) was added, extracted with diethyl ether (2 x 60 mL) and the organic solvent dried using magnesium sulfate and evaporated. The residue was distilled at 0.25 mmHg to obtain 3.06 g (51% yield,

35   b.p. 98-100°C)13-tetradecenyl chloride as a colourless liquid.

To a suspension of sodium theobromine (1.82 g, 8.68 mmol) in dimethylsulfoxide (20 mL) was added 13-tridecenyl chloride and the reaction stirred for 48 hours at 50°C. The mixture was then poured into water (60 mL) and extracted with ethyl acetate (3 x 50 mL). The organic portions were combined, dried using magnesium sulfate and evaporated to give a

cream solid. Recrystallization from hot hexane yields 2.38 g (73% yield) 1-(13-Tetradecenyl)-3,7-dimethylxanthine as a white solid.

A solution of 1-(13-Tetradecenyl)-3,7-dimethylxanthine (2.00 g, 5.35 mmol), 4-methylmorpholine-N-oxide (2.72 mL, 60% wt in water, 15.8 mmol) and potassium osmate

5   dihydrate (21 mg, 0.05 mmol) in acetone/water 3:1 (80 mL) was stirred for 16 hours. Water (100 mL) and sodium sulfite (1 g) were added and stirred for 1 hour. The reaction mixture was extracted with dichloromethane (3 x 100 mL) and the organic phase dried (magnesium sulfate) and evaporated to yield 2.10 g (96% yield) 1-(13,14-Dihydroxytetradecyl)-3,7-dimethylxanthine as a white solid.

10   1-(13,14-Dihydroxytetradecyl)-3,7-dimethylxanthine (0.80 g, 1.96 mmol) was stirred with HBr (1.94 mL of a 30% solution in acetic acid, 5.88 mmol) for 2 hours. The mixture was then added over 10 minutes to water (20 mL), ice (15 g) and NaHCO3 (3.5 g) and stirred for 30 minutes. The reaction mixture was extracted with dichloromethane (2 x 50 mL), the combined organic phases were dried using magnesium sulfate and the solvent was evaporated

15   to obtain a residue of 1-(13-acetoxy-14-bromotetradecyl)-3,7-dimethylxanthine.

Without further purification, this crude residue was taken up in methanol (5 mL) and treated with a solution of sodium methoxide (prepared from sodium (0.069 g, 3.00 mmol) and 5 mL methanol). After 40 minutes, the reaction was added to water (15 mL) and extracted with dichloromethane (3 x 30 mL). The organic portions were combined, dried and

20   the solvent evaporated to yield 0.71 g (93% yield) of 1-(13,14-Oxidotetradecyl)-3,7-dimethylxanthine as a white solid.

Example 46

This example illustrates a synthesis of 1-(16,17-Oxidoheptadecyl)-3,7-dimethylxanthine (CT-3516). To a suspension of magnesium (3.10 g, 129 mmol) and a

25   crystal of iodine in THF (10 mL) was added 10-undecenyl bromide (6.00 g, 25.8 mmol, available from MTM) in THF (20 mL) over 40 minutes and the reaction stirred for a further 30 minutes after the addition was complete. The solution was added via a canula over 50 minutes to a suspension of copper iodide (0.50 g, 2.58 mmol) and 1-bromo-6-chloro hexane (6.00 mL, 40.0 mmol) in THF (20 mL) and stirred at 25°C for 16 hours. Sulfuric acid (1.0

30   M, 50 mL) was added, extracted with diethyl ether (2 x 60 mL) and the organic solvent dried using magnesium sulfate and the solvent subsequently evaporated. The residue was distilled at 0.75 mmHg to yield 1.78 g (25% yield, b.p. 130-135°C) 16-heptadecenyl chloride as a colourless liquid.

To a suspension of sodium theobromine (2.02 g, 10.0 mmol) in dimethylsulfoxide/

35   tetrahydrofuran (2:1, 30 mL) was added 16-heptadecenyl chloride and the reaction stirred for 16 hours at 60°C. The mixture was poured into water (75 mL) and extracted with ethyl acetate (3 x 75 mL). The organic portions were combined, dried using magnesium sulfate, and the solvent evaporated to give a cream solid. Recrystallization from hot hexane yields 2.31 g (85% yield) 1-(16-Heptadecenyl)-3,7-dimethylxanthine as a white solid.

A solution of 1-(16-Heptadecenyl)-3,7-dimethylxanthine (1.50 g, 3.60 mmol), 4-methylmorpholine-N-oxide (1.83 mL, 60% wt in water, 10.6 mmol) and potassium osmate dihydrate (16 mg, 0.04 mmol) in acetone/water/ tetrahydrofuran (10:7:5, 110 mL) was stirred for 60 hours. Water (100 mL) and sodium sulfite (1 g) were added and the reaction mixture

5   stirred for 1 hour. The reaction mixture was extracted with dichloromethane (2 x 100 mL) and the organic phase dried using magnesium sulfate and the solvent evaporated to afford a cream solid. Recrystallization from hot ethyl acetate yields 1.31 g (81% yield) of 1-(16,17-dihydroxyheptadecyl)-3,7-dimethylxanthine (CT3514).

1-(16,17-Dihydroxyheptadecyl)-3,7-dimethylxanthine (1.10 g, 2.44 mmol) was

10 stirred with HBr (3.50 mL of a 30% solution in acetic acid, 17.1 mmol) for 4 hours. The mixture was then added over 10 minutes to water (50 mL),and NaHCO3 (10 g) and stirred for 30 minutes. The reaction mixture was extracted with dichloromethane (3 x 30 mL), the combined organic phases were dried using magnesium sulfate and the solvent was evaporated to obtain a residue of 1-(16-acetoxy-17-bromoheptadecyl)-3,7-dimethylxanthine.

15 Without further purification, 1-(16-acetoxy-17-bromoheptadecyl)-3,7-dimethylxanthine was taken up in methanol (5 mL) and treated with a solution of sodium methoxide (prepared from sodium (0.074 g, 3.20 mmol) and 5 mL methanol). After 40 minutes, the reaction mixture was added to water (15 mL) and extracted with dichloromethane (3 x 30 mL). The organic portions were combined, dried and the solvent

20 evaporated to 1.00 g (95% yield) 1-(16,17-Oxidoheptadecyl)-3,7-dimethylxanthine as a white solid.

Example 47

This example illustrates a synthesis of N-(5,6-Oxidohexylamido)glutaric acid, methyl ester (CT1301). Sodium hydride (425 mg, 17.7 mmol) was added to a solution of

25 glutarimide (2.00 g, 7.7 mmol) in dimethyl sulfoxide (40 mL). After 20 minutes of stirring, 6-bromo-1-hexene (2.90 g, 17.7 mmol) was added. After 20 hours of stirring, the reaction was poured into a separatory funnel containing 100 mL water and extracted with dichlormethane (4 X 50 mL). The organic portions were combined, washed with water (50 mL) and brine (50 mL) and dried to yield 2.92 g (85% yield) 1-(5-Hexenyl)glutarimide

30 (CT1600) as a colorless oil.

A solution of 1-(5-hexenyl)glutarimide (1.50 g, 7.7 mmol), 4-methylmorpholine-N-oxide (1.08 g, 9.2 mmol) and osmium tetraoxide (3 drops of a 2.5% sol. by wt. in *tert*-butanol) in acetone (10 mL) and water (10 mL) was stirred for 69 hours. Following addition of 10 mL of a saturated solution of sodium dithionite and a further 15 minutes of stirring, the

35 reaction was extracted with 25% ethanol/dichlormethane (4 X 50 mL). The organic layers were combined and dried (sodium sulfate) and evaporated to a thick oil which was purified by chromatography using silica and an ethyl acetate eluant to yield 1.29 g (73% yield) N-(5,6-Dihydroxyhexyl)glutarimide (CT1603) as a colorless oil.

47

To 1-(5,6-dihydroxyhexyl)glutarimide (1.29 g, 5.6 mmol) was added 30% hydrogen
bromide-acetic acid (3.4 mL) and the resulting mixture stirred until all of the solid had
dissolved (45 minutes). The solution was poured carefully over a mixture of sodium
bicarbonate (6.5 g), ice water (40 mL), and dichloromethane (40 mL). After carbon dioxide

5   evolution had subsided, the organic layer was separated, and the aqueous layer extracted with
dichloromethane (2 X 30 mL). The combined organic layers were dried over magnesium
sulfate and the solvent was evaporated under vacuum to yield 1.73 g (92% yield) 1-(5-
Acetoxy-6-bromohexyl)glutarimide as a viscous oil which was dissolved in methanol (5 mL).
A 0.7M sodium methoxide in methanol solution (6 mL) was added all at once. After stirring

10   for 15 minutes, the solution was treated with water (20 mL) and then extracted with
dichloromethane (3 X 15 mL). The combined extracts were dried over magnesium sulfate
and the solvents were evaporated under vacuum. The residue was chromatographed (80%
ethyl acetate/20% petroleum ether) to yield 256 mg (18% yield) N-(5,6-
Oxidohexylamido)glutaric acid, methyl ester as a colorless oil.

15   **Example 48**

This example illustrates the effects of CT1541 as hair growth stimulant in nude mice.
In a procedure similar to that used in a commercial model for predicting human hair-growing
ability of minoxidil, nu/nu (nude) mice were painted twice daily for 16 days on the right
flank with CT1541 using sterile applicators. Researches handled the mice under a laminar

20   flow hood with applicator, wearing face mask and sterile gloves.

After 16 days, one mouse was sacrificed by cervical dislocation and skin biopsies
taken from the treated areas of the shoulder/flank and the non-treated area of the dorsal pelvis
(rump). Specimens were placed in 10% buffered formalin solution.

A microscopic analysis of the skin biopsies confirmed that follicles in the treated

25   areas had hair shafts which sometimes exit to the surface. There were mild accumulations of
mixed inflammatory cells in the dermis. In contrast, hair follicles from untreated skin
biopsies were smaller/shorter and less often extend into the subcutis. Hair shafts were rarely
seen. A few mixed inflammatory cells were in the dermis in the untreated areas as well.

The treated sections had more normal appearing hair follicles than the untreated

30   sections. In addition, numerous hair shafts were seen exiting follicles in the treated sections.

Six weeks following treatment, a second mouse was euthanatized and biopsied the
same as previous mouse after 16 days.

A microscopic examination of the skin biopsies taken after six weeks confirmed hair
loss. The biopsies showed slightly more acanthosis (epidermal hyperplasta) in treated areas

35   and slightly straighter superficial portions of follicles with less curling of hair shafts. In
treated sections, the subcutis contained active anagen bulbs located deeply in the subcutis.
The follicles were slightly dilated. Scattered mast cells, lymphocytes and a few neutrophils
were present. One section had a few increased cells in the subcutis.

These data show that CT1541, when applied topically, can be used to treat or prevent baldness or allopecia.

Example 49

This example illustrates the effects of CT1105, CT1114, CT1413, CT1439, CT1594,
5   CT2518, CT2548R, CT2548S, CT2562 and CT3503 as effective inhibitors of IL-2 induced proliferation of thymocytes. Single cell suspensions of thymus gland cells obtained from 4-6 week old mice were prepared. Two-hundred thousand cells were plated into individual wells of flat-bottom 96-well plates in RPMI-1640-10% FCS medium. The invention compounds were then added to the wells at varying concentrations and the cells incubated for 1-2 hours
10 at 37°C.

Following this pre-incubation a mixture of Concanavalin A (ConA) and Interleukin-2 (IL2) was added to the experimental wells at a final concentration of (0.25ug/ml ConA)/(20 ng/ml IL2). Appropriate positive and negative controls were set up on each plate. Each variable was set up in quadruplicate.

15 The plates were incubated for 4 days at 37°C in a humidified CO_2 incubator. On day 4 the wells were pulsed with 1µCi of tritiated thymidine(3H-TdR) and the plates incubated for an additional 4 hours. The plates were then harvested and the incorporation of 3H-TdR was determined in a liquid scintillation counter. From the CPM obtained from each experimental well an IC-50 for each inventive compound tested was determined. Therefore,
20 a lower reported IC-50 value is indicative of greater inhibition of IL-2-induced proliferation of thymocytes. Table II illustrates IC-50 values (in µM) for inventive compounds inhibiting proliferation at very low concentrations of compound.

Table II

Inventive Compound	IC-50 (µM)
CT2562	3.1
CT2518	3.4
CT2548S	4.6
CT2548R	7.5
CT1413	7.7
CT1439	8.0
CT1105	8.5
CT1594	8.5
CT1114	10.0
CT3503	10.0

These data show that the illustrated inventive compounds are effective therapeutic
25 agents for the treatment or prevention of autoimune disorders or inflammatory diseases.

<u>Example 50</u>

This example illustrates the effects of CT1114, CT1413, CT1560, CT1565, CT1594, CT2518, CT2548R, CT2548S and CT3503 as effective inhibitors of normal human bone marrow stromal cells (MSC) proliferation in response to Platelet Derived Growth Factor BB (PDGF B) and IL-1α (50 and 10 ng/ml, respectively). Maximum proliferation occurs when both PDGF B and IL-1α are present, hence a combination of both were used in the following assay.

MSC were obtained and maintained in exponential growth, released from a growth plate with trypsin and plated into 96 well tissue culture plates in the presence of Fibroblast Growth Factor (FGFβ) for 48 hours. Growth media were removed and the cells were washed once with serum free media. The cells were then incubated 20-24 hours in serum free media.

After incubation, inventive compounds were added to the cells at the appropriate concentration and then the cells again incubated for 1 hour. PDGF B and IL-1α were added to the cells along with 3H-thymidine and the cells again incubated for an additional 24 hours.

After 24 hours of incubation, the cells were then harvested to assess incorporation of ^{3}H-thymidine into DNA (proliferation). From each harvested cell culture, an IC-50 for each inventive compound tested was determined. Therefore, a lower reported IC-50 value is indicative of greater activity of the invention compounds in inhibiting MSC proliferation. Table III illustrates IC-50 values (in μM) for invention compounds inhibiting MSC proliferation at very low concentrations of compound.

<u>Table III</u>

Inventive Compound	IC-50 (μM)
CT1413	3.7
CT1114	5.1
CT2548S	5.9
CT1560	6.6
CT2548R	8.7
CT1594	14.0
CT3503	14.0
CT2518	16.7
CT1565	17.0
CT1539	18.0

These data illustrate the inventive compounds illustrated are usefule to treat or prevent restenosis and atheroscherosis

<u>Example 51</u>

This example illustrates the effects of CT1605, CT1808 and CT1906 as immune modulators in a mixed lymphocyte reaction. Figure 1 shows the effects of three inventive compounds CT1605 (N-(5,6-oxidohexyl) glutarimide), CT1808 (N^3-(5,6oxidohexyl)-N^1-

methyluracil), and CT1906 (N^3-(5,6-oxidohexyl) N^1-methylthymine. The mixed lymphocyte reaction shows a proliferative response of PBMC (peripheral blood mononuclear cells) to allogeneic stimulation determined in a two-way mixed lymphocyte reaction. Each of the inventive compounds tested demonstrated activity in this immune modulating activity assay procedure.

Example 52

This example illustrates a comparison of three dose levels of CT1808 and CT1906 and no drug control to inhibit thymocyte proliferation. The thymocytes were obtained from normal female Balb/C mice and stimulated with Concanavalin A (Con A) and/or IL-1α (interleukin-1 alpha). The thymuses were dissociated and plated into 96-well plates at a density of 2 x 10^5 cells/well. Dilutions of Con A and/or IL-1α were added to the wells and the cells were incubated for 4 days at 37°C. Drugs were added to the cell cultures two hours before activation with Con A and/or IL-1α. On day 4, the cells were pulsed with tritiated thymidine and allowed to incubate an additional 4 hrs. The cells were harvested and counted. As shown in Figure 2, both drugs inhibited thymocyte proliferation is a dose-dependent fashion.

Example 53

This example illustrates a comparison of CT1605 and CT1808 for inhibition of B-cell proliferation. A Ramos C-cell tumor line was treated with 250 μM CT1808 or CT1605 for one hour prior to stimulation of proliferation with anti-mu antibody or PMA (5 nM). One day later, proliferation was measured with tritiated thymidine. As shown in Figure 3, both CT1605 and CT1808 inhibited proliferation in this model.

Example 54

This example illustrates a comparison of CT1605, CT1808 and CT1906 on PDGF-induced (platelet derived growth factor) proliferation of human stromal cells. Human stromal cells were starved in serum-free media for 24 hours and then stimulated with 50 ng/ml of PDGF-BB. The drugs were added at various indicated concentrations one hour prior to PDGF stimulation. Tritiated thymidine was added for 24 hrs at the time of PDGF stimulation to measure cellular proliferation. Background counts were approximately 5% of control levels. As shown in Figure 4, all three drugs inhibited PDGF-induced stimulation in a dose response fashion.

Example 55

This example illustrates a comparison of the effects of CT1605, CT1808 and CT1906 to inhibit adhesion of U937 cells to activated human umbilical vein endothelial cells (HUVEC). HUVEC cells (4000/well, seeded 72 hrs in advance) were activated with 20 ng/ml of TNF for 12 hrs. Drug was added to each culture (except for controls) one hour prior to adding TNF. U937 cells, preloaded with the fluorescent dye BCECF, were added to each culture well and then washed twice with PBS. Cell adhesion was determined by

measuring fluorescence on a fluorescence plate reader. As illustrated in Figure 5, all three
drugs showed a decrease in cell adhesion caused in a dose dependent fashion

Example 56

       This example illustrates the effects of CT1605, CT1808 and CT1906 to inhibit cell

5   surface expression of VCAM in human umbilical vein endothelial cells (HUVEC). The
HUVEC cells were stimulated with 20 ng/ml TNF-α for 20 hrs and then stained for
immunofluorescence using a monoclonal antibody recognizing VCAM, followed by a goat
anti-mouse antibody conjugated to phycoerythrin. The cells were analyzed for antibody
binding using flow cytometry. Figure 6 shows an analysis of mean relative fluorescence

10   intensity of 10,000 cells, analyzed by flow cytometry. The mean fluorescence levels were
decreased by all three drugs from control levels (TNF treatment, no drug).

Claims

We claim:

1.   A compound having immune modulating activity, comprising an epoxide-substituted alkyl side chain bonded to a heterocyclic or a non-heterocyclic core moiety, said compound having the following general structure:
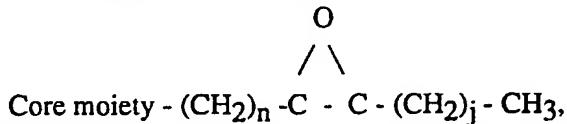
$$\text{Core moiety - (CH}_2)_n \text{ -C } \overset{\displaystyle \overset{O}{/\ \backslash}}{-} \text{ C - (CH}_2)_j \text{ - CH}_3,$$

wherein n is an integer from about 4 to about 16 and j is an integer from about 0 to about 12, wherein the alkyl group $(CH_2)_n$ may be substituted by a hydroxyl, halogen, oxygen, a (C_{1-4}) alkyl group or a dimethylamino group, including resolved enantiomers, diastereomers, slovates, hydrates, or salts thereof.

2.   The compound according to claim 1, wherein the non-heterocyclic core moiety is selected from the group consisting of: one or two amino acids; an hydroxyl group; a carboxyl group; a sulfoxide group; a sulfonate group; a phosphate group; an amide; an amine; a ketone; a simple ionic functional group; a terminal hydrogen and a halogen atom (bromine, chlorine, fluorine or iodine) and wherein amino acids are selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

3.   The compound according to claim 1, wherein the heterocyclic core moiety is a member selected from the group consisting of substituted or unsubstituted phthalimide, homophthalimide, quinazolidinedione, quinazoline, xanthine, glutarimide, piperidine, piperidone, γ-valerolactam, cyclohexane, cyclohexene, benzene, uracil, thymine, uracil fused to napthalene, ortho-phenol, imidazole amide, pyrrole amide, benzamide, tetrahydrophthalimide, succinimide, 1,7-methylxanthine, 8-amino-3-methylxanthine, 7-methylhypoxanthine, dimethyldihydroxypyrazolo[4,3-d]pyrimidine, methylpyrrolo[2,3-d]pyrimidine, 5- and 6- substituted uracils, 6-aminouracil, 2,4-dioxohexahydro-1,3,5-triazine, methylbarbituric acid, isocarbostyril, 1,2,3,4-tetrahydroisoquinolin, 2-hydroxypyridine, 3,3-dimethylflutarimide, 1,3-dihydroxynapthalene, 1,3-cyclopentanedione, 2-pyrrole amide, 3-pyrrole amide, 1-pyrrole amide and substituted benzamides.

4.   The compound according to claim 1, wherein the compound is selected from the group consisting of N-(5,6-Oxidohexyl)phthalimide, N-(8,9-Oxidononyl)phthalimide, N-(10,11-Oxidoundecyl)phthalimide, N-(10,11-Oxidoundecyl)homophthalimide, 1-(5,6-Oxidohexyl)-3-methylbenzoyleneurea, N-(5,6-Oxidohexylamido)glutaric acid (methyl ester), 1-(8,9-Oxidononyl)-3-methyl-7-methylpivaloylxanthine, 1-(5,6-Oxidononyl)-3-methyl-7-methylpivaloylxanthine, 1-(11,10-Oxidoundecyl)-3-methyl-7-methylpivaloylxanthine, 1-(7,8-Oxidooctyl)-3,7-dimethylxanthine, 1-(7,8-Oxidooctyl)-3,7-dimethylxanthine, 1-(4,5-Oxidohexyl)-3,7-dimethylxanthine, 1-(8,9-Oxidononyl)-3,7-dimethylxanthine, 1-(9,10-

Oxidodecyl)-3,7-dimethylxanthine, 1-(6,7-*trans*-Oxidononyl)-3,7-dimethylxanthine, 1-(6,7-Oxidoheptyl)-3,7-dimethylxanthine, 1-(3-(R)-Methyl-7-methyl-(6,7-oxidooctyl)-3,7-dimethylxanthine, 1-(4,5-Oxidopentyl)-3,7-dimethylxanthine, 1-(7,8-Oxidoundecyl)-3,7-dimethylxanthine, N-(5,6-Oxidohexyl)glutarimide, N-(8,9-Oxidononyl)glutarimide, N-

5   (10,11Oxidoundecyl)glutarimide, N-(10,11-Oxidoundecyl)-2-pieridone, N-(5,6-Oxidohexyl)piperidine, 3-(8,9-Oxidononyl)-1-methyluracil, 3-(5,6-Oxidohexyl)-1-methyluracil, 3-(5,6-Oxidoheyl)-1-methyldihydrouracil, 3-(10,11-Oxidoundecyl)-1-methyldihydrouracil, 3-(5,6-Oxidohexyl)-1-methylthymine, 3-(8,9-Oxidononyl)-1-methylthymine, 3-(11,10-Oxidoundecyl)-1-methylthymine, 1-(3,4-Oxidobutyl)-3,7-

10 dimethylxanthine, 1-(11,12-Oxidodecyl)-3,7-dimethylxanthine, 1-(9,10-Oxidooctadecyl)-3,7-dimethylxanthine, 1-(4-Methyl-7,8-oxido-8-methylnonyl)-3,7-dimethylxanthine, 1-(3,7-dimethyl-2,3,6,7-dioxidooctyl)-3,7-dimethylxanthine, 1-(12,13-Oxidotridecyl)-3,7-dimethylxanthine, 1-(7,8-*cis*-Oxidodecyl)-3,7-dimethylxanthine, 1-(13,14-Oxidotetradecyl)-3,7-dimethylxanthine, and 1-(16,17-Oxidoheptadecyl)-3,7-dimethylxanthine.

15   5.   A pharmaceutical composition comprising a compound of claim 1 in admixture with a pharmaceutically acceptable excipient or carrier.

        6.   A method to modulate cellular metabolism in a subject, wherein said modulation is desirable to mitigate a condition of said subject, which method comprises administering to said subject a therapeutically effective amount of a compound of claim 1 or

20 a pharmaceutical composition thereof, wherein said condition is selected from the group consisting of a tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, mucositis, allergic response, and disorders of the central nervous system.

25   7.   A method for treating or preventing sepsis syndrome, including septic shock, to a patient exhibiting shock-like symptoms or to a patient in need of prophylactic treatment of sepsis syndrome, comprising administering an effective amount of a compound of claim 1 or a pharmaceutical composition thereof.

        8.   A method for treating or preventing hematopoietic or organ toxicity caused by

30 cytoreductive therapies to a patient in need of such treatment, comprising administering an effective amount of a compound of claim 1 or a pharmaceutical composition thereof.

        9.   A method for treating or preventing baldness, hair loss or allopecia caused by cytoreductive therapies to a patient in need of such treatment, comprising administering an effective amount of a compound of claim 1 or a pharmaceutical composition thereof.

35   10.   A method for treating or preventing the progression of an inflammatory disease or an autoimmune disease to a patient in need of such a treatment, comprising administering an effective amount of a compound of claim 1 or a pharmaceutical composition thereof.
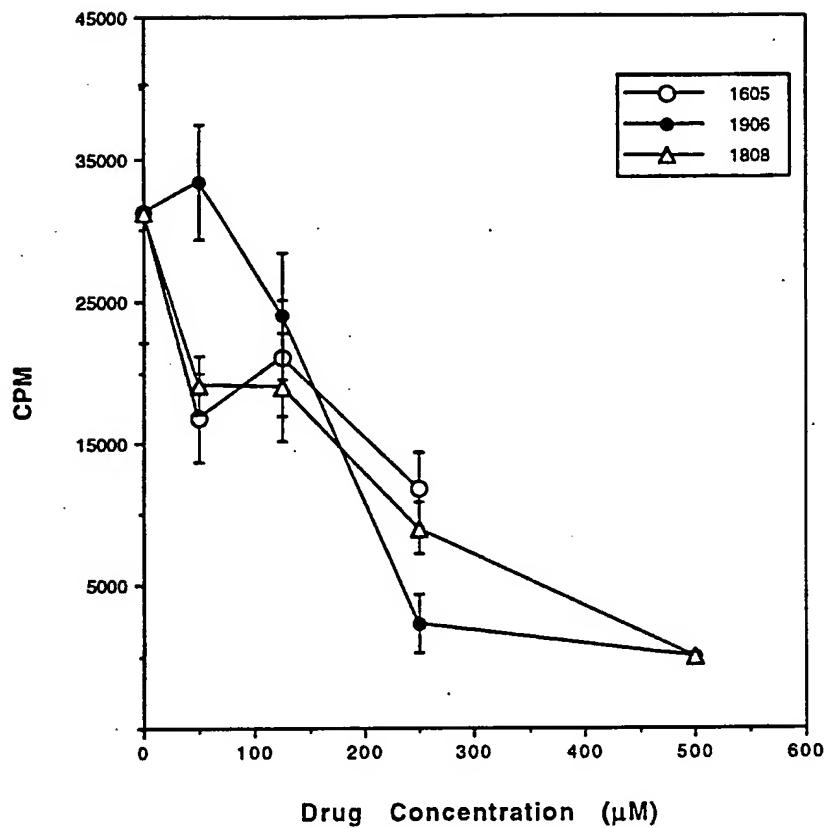
Figure 1
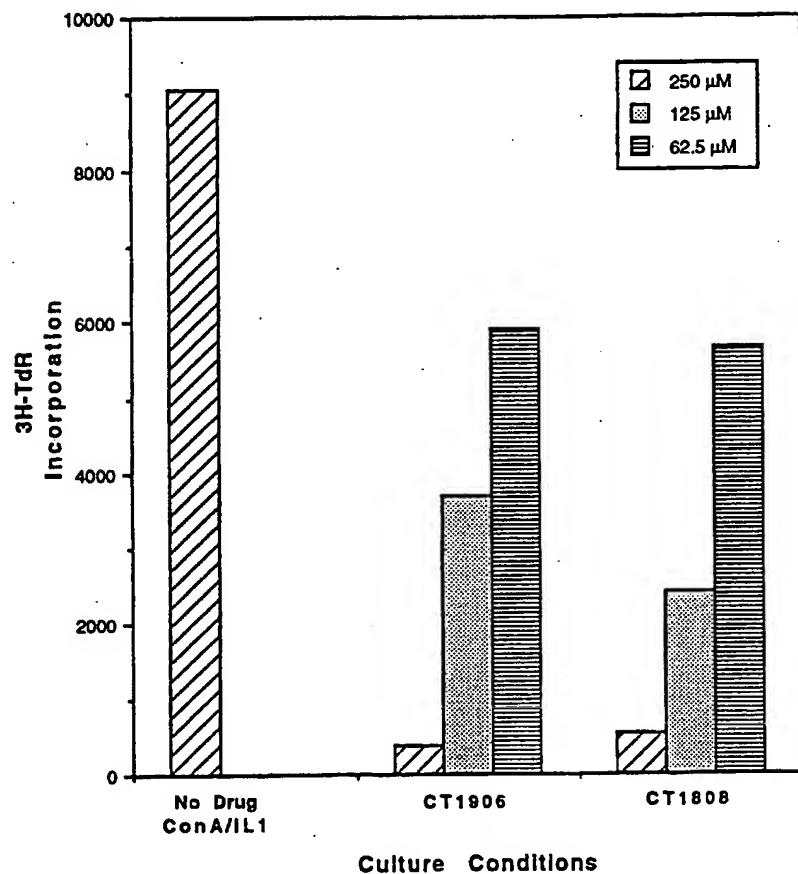
Figure 2

Figure 3

Figure 4

SUBSTITUTE SHEET

Figure 5

Figure 6

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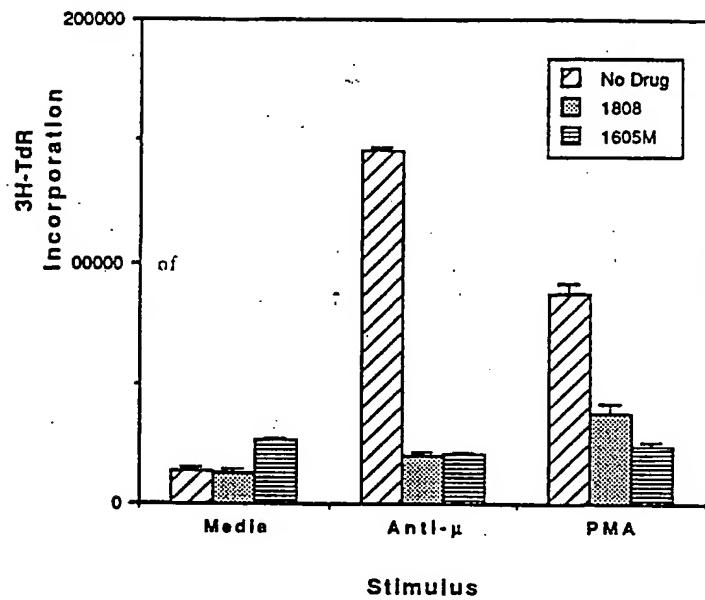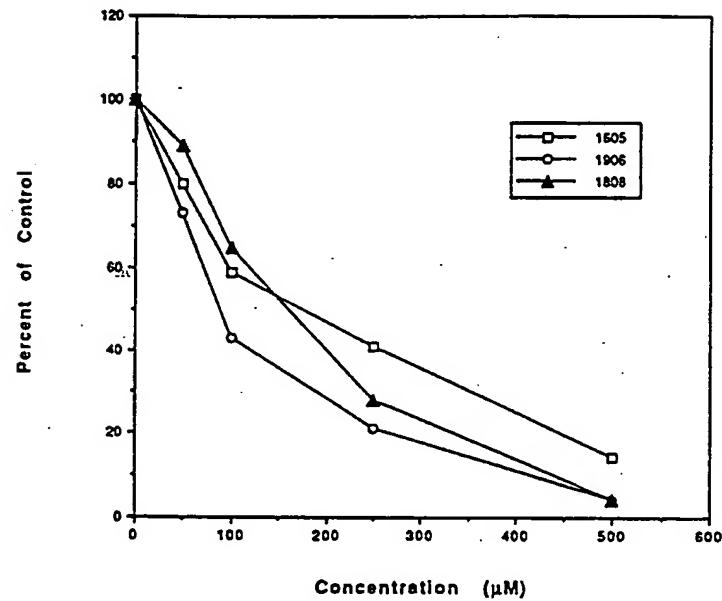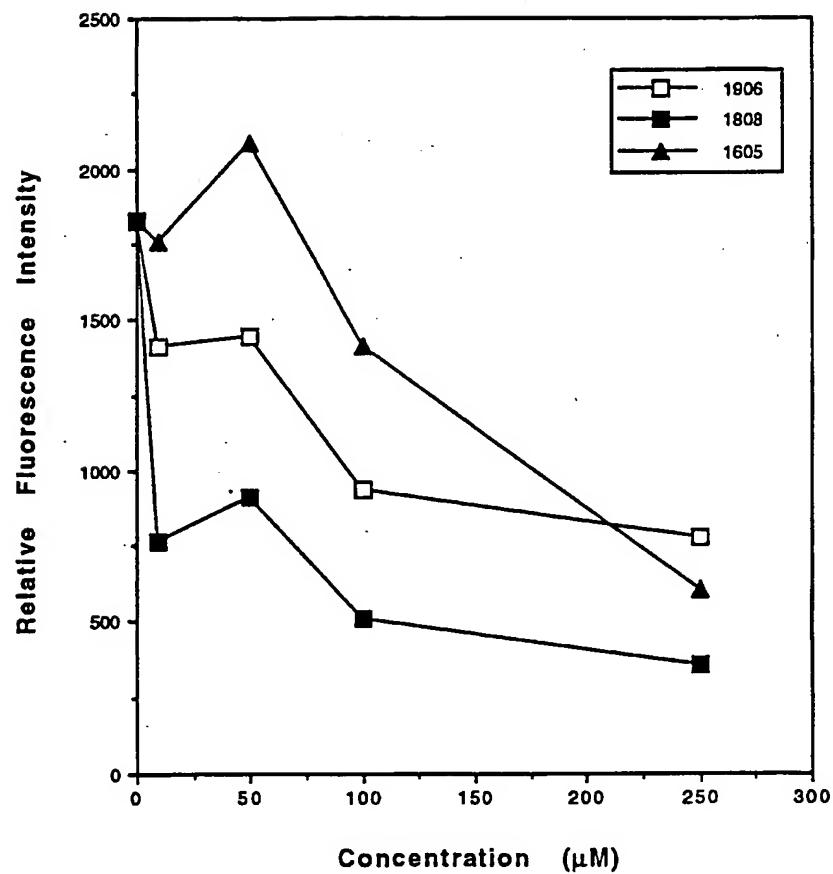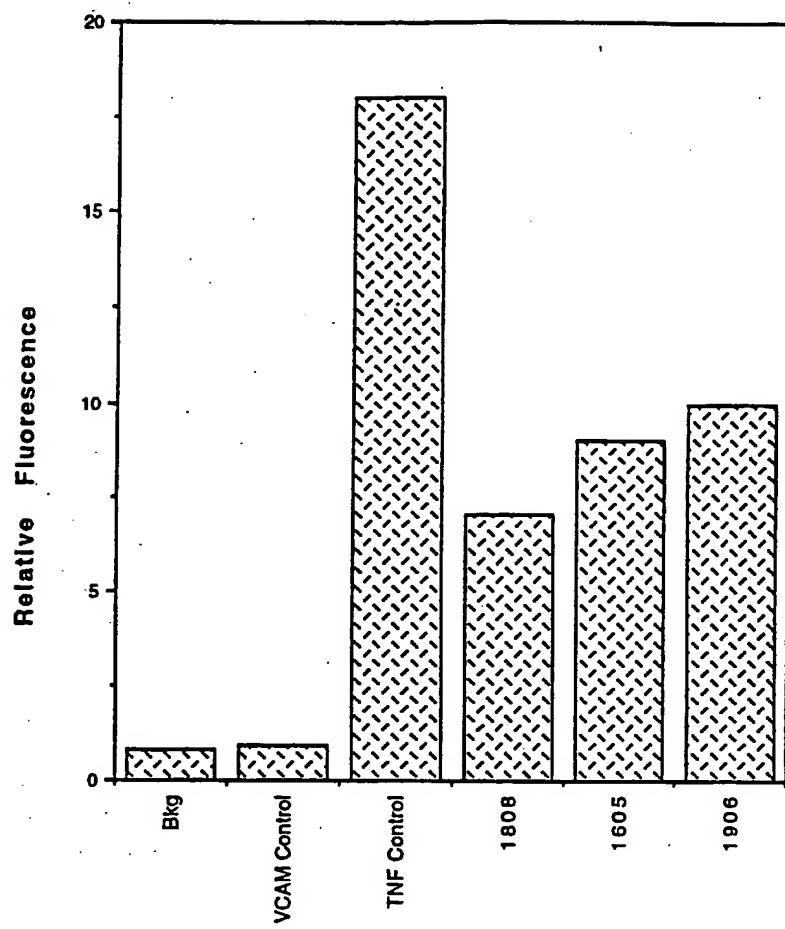
INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/09073

A.	CLASSIFICATION OF SUBJECT MATTER

IPC(5)   :A61K 31/52; C07D 239/46
US CL   :514/183; 544/267; 549/512

According to International Patent Classification (IPC) or to both national classification and IPC

B.	FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :   514/183; 544/267; 549/512

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE: Structure Search

C.	DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACT., Vol. 99, issued 1983, AKHMEDOV et al.,"STUDY OF THE REACTION OF UNSATURATED CHLORIDE - CONTAINING EPOXY COMPOUNDS WITH SECONDARY AMINES", see Abstract No. 99:158152e.	1-6, 9, 10
X	JOURNAL OF ORGANIC CHEMISTRY, Vol. 47, issued 1982, JAKUBOWSKI et al., "Total synthesis of ($\pm$)-Cerulenin, ($\pm$) - TETRAHYDROCERULENIN, and Related Compounds", pages 1221-1227, see page 1224 27) b, c and 26) b, c; and page 1227, lines 9 and 10.	1-6, 9, 10
A,P	US, A, 5,158,967 (HALL) 27 OCTOBER 1992. SEE ABSTRACT.	6, 9, 10

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 DECEMBER 1993	09 FEB 1994

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	P.K. SRIPADA ACH
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
        (Telephone Practice)
   Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
   1-6 (in part) wherein compounds containing a heterocyclic core, 9 and 10

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

In the examination of international applications filed under the Patent Cooperation Treaty, PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions having a special technical relationship.

Additionally, current United States Patent and Trademark Office restriction practice permits the following combinations of the claimed invention:

a product, and a process specifically adapted for the manufacture of said product, and

a product, and a use of the said product, as where said use as claimed cannot be practiced with another materially different product.

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

I. Claims 1-6 (in part) and 10; drawn to epoxides attached to heterocyclic core; compositions and method of treating inflammatory or unwanted immune response; autoimmune disease and allergic response; Classes 544; 514 subclasses 267 (+others); 183.

II. Claims 1-6 (in part); drawn to epoxides attached to non-heterocyclic core and compositions. Class 549; subclasses 512; 514.

III. Claim 9; drawn to method of treating baldness; and compositions. Class 514, subclass 183.

IV. Claim 7; drawn to method of treating sepsis syndrome; Class 514, subclass 183.

V. Claims 6 (in part) and 8; drawn to treating tumor burden or organ toxicity; Class 514; subclass 183.

VI. Claim 6 (in part) drawn to hormone-related disorder; Class 514; subclass 183;

VII. Claim 6 (in part) drawn to neurological disorder and central nervous system disorders. Class 514; subclass 183.

VIII. Claim 6 (in part); drawn to viral infection; Class 514; subclass 183;

IX. Claim 6 (in part) drawn to hypertension Class 514, subclass 183;

X. Claim 6 (in part) drawn to Nephritis, Class 514, subclass 183;

XI. Claim 6 (in part) drawn to mucositis, Class 514, subclass 183;

XII. Claim 6 (in part); drawn to restinosis; Class 514, subclass 183;

Reasons For Lack Of Unity:

The inventions listed as Groups I-XII are drawn to epoxide attached to compounds with heterocyclic and non-heterocyclic cores. Thus, there is no common technical feature' between I and II and hence they lack unity of invention. Similarly III to XII are drawn to different methods of use. If one of inventions, III i.e., treatment of baldness is found in the prior art, it would not make other methods of treatment, IV to XII obviously do not meet the requirements for Unity of Invention for the above reasons.